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Principles of Cancer Chemotherapy

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Introduction

The development of chemotherapy in the 1950s and 1960s resulted in curative therapeutic strategies for patients with hematologic malignancies and several types of advanced solid tumors. These advances confirmed the principle that chemotherapy could indeed cure cancer, and provided rationale for integrating chemotherapy into combined modality programs with surgery and radiation therapy in early stages of disease so as to provide clinical benefit. The principal obstacles to the clinical efficacy of chemotherapy have been toxicity to the normal tissues of the body and the development of cellular drug resistance. The development and application of molecular techniques to analyze gene expression of normal and malignant cells at the level of DNA, RNA, and/or protein has helped to identify some of the critical mechanisms through which chemotherapy exerts its antitumor effects and activates the program of cell death. This modern-day technology has also provided insights into the molecular and genetic events within cancer cells that can confer chemosensitivity to drug treatment. This enhanced understanding of the molecular pathways by which chemotherapy exerts its cytotoxic activity and by which genetic change can result in resistance to drug therapy has provided rationale for developing innovative therapeutic strategies in which molecular, genetic, and biologic therapies can be used in combination to directly attack these novel targets. As we now move forward in this new millennium, the implementation of such novel treatment approaches provides an important paradigm shift in which therapy is administered. The long-term goal of these intense research efforts is to improve the clinical outcome of cancer patients undergoing treatment, especially in those with cancers that have been traditionally resistant to conventional chemotherapy.

The Role of Chemotherapy in the Treatment of Cancer

Chemotherapy is presently used in four main clinical settings: (1) primary induction treatment for advanced disease or for cancers for which there are no other effective treatment approaches, (2) neoadjuvant treatment for patients who present with localized disease, for whom local forms of therapy, such as surgery and/or radiation are inadequate by themselves, (3) adjuvant treatment to local methods of treatment, including surgery and/or radiation therapy, and (4) direct instillation into sanctuary sites or by site-directed perfusion of specific regions of the body directly affected by the cancer.

Primary induction chemotherapy refers to drug therapy administered as the primary treatment for patients who present with advanced cancer for which no alternative treatment exists.[1,2] This has been the mainstay approach to treat patients with advanced, metastatic disease, and in most cases, the goals of therapy are to palliate tumor-related symptoms, improve overall quality of life, and prolong time to tumor progression and survival. Studies in a wide range of solid tumors have clearly shown that chemotherapy in patients with advanced disease confers survival benefit when compared to supportive care, providing sound rationale for the early initiation of drug treatment. Cancer chemotherapy can be curative in a relatively small subset of patients who present with advanced disease. In adults, these curative cancers include Hodgkin's and non-Hodgkin's lymphoma, germ cell cancer, and choriocarcinoma, while the curative childhood cancers include acute lymphoblastic leukemia, Burkitt's lymphoma, Wilms' tumor, and embryonal rhabdomyosarcoma.

Neoadjuvant chemotherapy refers to the use of chemotherapy for patients who present with localized cancer for which alternative local therapies, such as surgery, exist but that they are less than completely effective.[3] For chemotherapy to be used as the initial treatment of a cancer, which would be partially curable by either surgery or radiation therapy, there must be documented evidence for its clinical efficacy in the advanced disease setting. At present, neoadjuvant therapy is most often administered in the treatment of anal cancer, bladder cancer, breast cancer, esophageal cancer, laryngeal cancer, locally advanced non-small cell lung cancer, and osteogenic sarcoma. For some of these diseases, such as anal cancer, gastro-esophageal cancer, laryngeal cancer, and non-small cell lung cancer, optimal clinical benefit is derived when chemotherapy is administered with radiation therapy either concurrently or sequentially.

One of the most important roles for cancer chemotherapy is as an adjuvant to local treatment modalities such as surgery and/or radiation therapy, and this has been termed adjuvant chemotherapy.[4] The development of disease recurrence, either locally or systemically, following surgery and/or radiation is mainly due to the spread of occult micrometastases. Thus, the goal of adjuvant therapy is to reduce the incidence of both local and systemic recurrence and to improve the overall survival of patients. In general, chemotherapy regimens with clinical activity

against advanced disease may have curative potential following surgical resection of the primary tumor, provided the appropriate dose and schedule are administered. Several well-conducted, randomized phase III clinical studies have documented that adjuvant chemotherapy is effective in prolonging both disease-free (DFS) and overall survival (OS) in patients with breast cancer, colon cancer, gastric cancer, non-small cell lung cancer, Wilms' tumor, and osteogenic sarcoma. There is also evidence to support the use of adjuvant chemotherapy in patients with anaplastic astrocytomas. Patients with primary malignant melanoma at high risk of metastases derive benefit in terms of improved DFS and OS from adjuvant treatment with the biologic agent α-interferon, although this treatment must be given for one year's duration for maximal clinical efficacy. Finally, the anti-estrogen tamoxifen is an effective adjuvant in post-menopausal women whose breast tumors express the estrogen receptor. However, because this agent is cytostatic rather than cytocidal, adjuvant therapy with tamoxifen must be administered on a long-term basis, with the standard recommendation being 5 years' duration.

Clinical Endpoints in Evaluating Response to Chemotherapy

In induction chemotherapy for patients with advanced cancer and measurable disease, it is possible to assess response to drugs on an individual basis. Partial response is defined as the fraction of patients who demonstrate at least a 50% reduction in measurable tumor mass. There is growing evidence to suggest that quality-of-life indices are improved in patients who show either a response to therapy or a minimal response as compared to supportive care, even when overall survival is not improved. However, partial responses are also useful in the evaluation of new drugs or new drug regimens, to determine whether a specific experimental approach is worthy of further clinical development.

It is clear, however, that the most important indicator of the effectiveness of chemotherapy is the complete response rate.[5] No patient with advanced cancer has ever been cured without first achieving a complete remission. In support of this concept is the fact that the recent advances seen in the treatment of advanced colorectal, breast, and non-small cell lung cancer have brought significant improvements in overall response rates and survival, yet have not translated into actual cure for these respective diseases; the reason being that the complete response rate for even these newer regimens has been uniformly less than 10%. When new anticancer drugs alone or in combination with other agents consistently produce more than an occasional complete remission, they have invariably been proven to have significant clinical benefit in medical practice. Thus, in clinical trials, complete and partial responses should always be reported separately. The most important indicator of the quality of a complete remission is the relapse-free survival from the time treatment is discontinued. This criterion is the only clinical counterpart of the quantifiable cytoreductive effect of drugs in in vivo preclinical models. The use

of freedom from progression in patients who have attained a mixture of complete and partial responses can be misleading when evaluating a new treatment. This method of analyzing clinical outcomes is a relatively simple indicator of the practical potential of a new treatment. However, for experimental treatments, it obscures the value of a relapse-free survival of complete responders as the major determinant of the quality of remission and the potential for cure. Other clinical end points, such as median response duration and median survival, while used in clinical trial design, are also of little practical value until treatment results have been refined to a point where complete response rates are higher than 50%.

The unique feature of administering chemotherapy in cancer patients with localized disease before or in place of strictly local treatments, such as surgery, radiation therapy, or both, is the preservation of the presenting tumor mass as a biologic marker of chemosensitivity to the drugs. Moreover, this approach has allowed the sparing of vital normal organs, including the larynx, the anal sphincter, and the bladder, as the primary tumor is reduced in size and rendered easier to deal with by traditional local modalities, such as surgery. As with induction chemotherapy for patients with advanced cancer, it is possible to determine the potential efficacy of a new treatment program on an individual basis. A good response to chemotherapy identifies a patient who may benefit from further treatment. In contrast, a poor response of the primary tumor to chemotherapy identifies a patient for whom alternative methods of treatment should be seriously considered. Another feature of primary neoadjuvant chemotherapy is the ability to differentiate partial responders with varying degrees of prognosis. Removal of residual tumor masses and histologic examination of the tissue allow determination of the viability and character of the remaining tumor cells. The response duration of complete and partial responders must be catalogued separately. Such an approach could result in shorter, less morbid, and more effective treatment programs. One of the other positive aspects of neoadjuvant chemotherapy is that it may be effective in killing micrometastatic disease that is present locally, systemically, or both. Given this fact, complete extent of disease may not be entirely clear with respect to loco-regional lymph node status when chemotherapy is administered in the pre-operative setting either alone or concurrently with radiation therapy. As in the case of locally advanced rectal cancer, additional cycles of chemotherapy are mandated to reduce the incidence of both local and systemic recurrence.

The rationale for adjuvant chemotherapy is to treat micrometastatic disease at a time when tumor burden is at a minimum, thereby enhancing the potential efficacy of drug treatment. It was assumed that chemotherapy, when administered at such an early stage, would result in significantly higher cure rates.[6,7] Unfortunately, because the primary tumor has already been removed, the major indicator of clinical efficacy of a chemotherapy program—the complete remission rate—is absent in the adjuvant setting. Treatment is selected for individual patients based on response rates experienced in an entirely different population, namely that of patients with advanced disease of the same histologic type. In adjuvant programs, relapse-free and overall survival remain the major end-

points. The relapse-free survival in the adjuvant setting measures time to regrowth to clinically detectable levels of cells unresponsive, partially responsive, or exquisitely sensitive to chemotherapy, and this endpoint is the equivalent of the duration of remission of a combined group of complete responders, partial responders, and non-responders. Of note, a recent analysis of adjuvant clinical studies for early-stage colon cancer conducted in the U.S. and Europe has suggested that the vast majority of relapses occurs within the first three years after completion of adjuvant therapy. These findings provide rationale for considering 3-year disease-free survival as the primary endpoint in adjuvant clinical trials of primary colon cancer.

Kinetics of Tumor Cell Growth

The key principles of chemotherapy were initially developed by Skipper et al.[8,9] using the murine leukemia L1210 cells as their experimental model system. However, drug treatment of human cancers requires a clear understanding of the differences between the growth characteristics of this rodent leukemia and of human cancers as well as an understanding of the differences in growth rates of normal target tissues between mice and humans. For example, L1210 is a rapidly growing leukemia with a high percentage of cells synthesizing DNA, as measured by the uptake of tritiated thymidine (the labeling index). Because L1210 leukemia has a growth fraction of 100% (i.e., all its cells are actively progressing through the cell cycle), its life cycle is consistent and predictable.

Based on the murine L1210 model, the cytotoxic effects of anticancer drugs follow log cell-kill kinetics. In general, a given agent would be predicted to kill a constant fraction of cells as opposed to a constant number. Thus, if an individual drug leads to a 3 log kill of cancer cells and reduces the tumor burden from 10^{10} to 10^{7} cells, the same dose used at a tumor burden of 10^{5} cells reduces the tumor mass to 10^{2}. Cell kill is, therefore, proportional, regardless of tumor burden. When treatment failed in sensitive cell lines, it was because the initial tumor burden was too high for even potentially curative doses of chemotherapy to eradicate the very last leukemia cell. The cardinal rule of chemotherapy—the invariable inverse relation between cell number and curability—was established with this model, and this relationship can be applied to other model systems, including both hematologic malignancies and solid tumors.

Although growth of murine leukemias simulates exponential cell kinetics, mathematical modeling data suggest that most human solid tumors do not grow in such an exponential manner. Taken together, the experimental data in human solid cancers support a Gompertzian model of tumor growth and regression. The critical distinction between Gompertzian and exponential growth is that in Gompertzian kinetics, the growth fraction of the tumor is not constant but decreases exponentially with time (exponential growth is matched by exponential retardation of growth). The growth fraction peaks when the tumor is approximately 37% of its maximum size. Under the Gompertzian model, when a patient

with advanced cancer is treated, the tumor mass is larger, its growth fraction is low, and the fraction of cells killed is, therefore, small. An important feature of Gompertzian growth is that response to chemotherapy in drug-sensitive tumors depends, in large measure, on where the tumor is in its particular growth curve.

Predictions can be made about the behavior of small tumors, such as would be the case with microscopic tumor burdens present after primary surgical therapy. When the tumor is clinically undetectable, its growth fraction would be at its highest level and, although the numerical reduction in cell number is small, the fractional cell kill from a known-to-be-effective therapeutic dose of chemotherapy would be significantly higher than later in the tumor course. This observation was initially used to justify dose reductions at lower tumor volumes. However, such an unnecessary dose reduction may account for some of the disappointment in the outcome of adjuvant studies in early-stage breast cancer. The Gompertzian model for tumor growth is important in that it can help to predict patterns of regrowth of residual tumor cells. Norton[10] analyzed the clinical data from multiple adjuvant studies for primary breast cancer and from available studies of untreated patients with localized disease. In each clinical study, the Gompertzian model precisely fit the growth curves of these tumors. In the adjuvant setting, the model predicted that relapse-free survival and survival curves are unable to discriminate between residual cell populations of only one cell and a residual population of 1 million cells, because the regrowth of residual cell populations will be faster at smaller volumes than it will be at larger volumes, producing identical results sometimes at 5 years after diagnosis and treatment. These findings suggest that short of total eradication of micrometastases (cure), varying residual volumes produce similar 5-year relapse-free survival and obscure the major differences in tumor reduction by different programs.

Principles of Combination Chemotherapy

With rare exceptions (e.g., choriocarcinoma and Burkitt's lymphoma), single drugs at clinically tolerable doses have been unable to cure cancer. In the 1960s and early 1970s, drug combination regimens were developed based on known biochemical actions of available anticancer drugs rather than on their clinical efficacy. Such regimens were, however, largely ineffective.[11,12] The era of effective combination chemotherapy began when a number of active drugs from different classes became available for use in combination in the treatment of the acute leukemias and lymphomas. Following this initial success with hematologic malignancies, combination chemotherapy was extended to the treatment of solid tumors.

Combination chemotherapy with conventional cytotoxic agents accomplishes several important objectives not possible with single-agent therapy. First, it provides maximal cell kill within the range of toxicity tolerated by the host for each drug as long as dosing is not compromised. Second, it provides a broader range of interaction between drugs and tumor cells with different genetic abnormalities in a heterogeneous tumor

population. Finally, it may prevent and/or slow the subsequent development of cellular drug resistance.

Certain principles have been useful in guiding the selection of drugs in the most effective drug combinations, and they provide a paradigm for the development of new drug therapeutic programs. First, only drugs known to be partially effective against the same tumor when used alone should be selected for use in combination. If available, drugs that produce some fraction of complete remission are preferred to those that produce only partial responses. Second, when several drugs of a class are available and are equally effective, a drug should be selected on the basis of toxicity that does not overlap with the toxicity of other drugs to be used in the combination. Although such selection leads to a wider range of side effects, it minimizes the risk of a lethal effect caused by multiple insults to the same organ system by different drugs and allows dose intensity to be maximized. In addition, drugs should be used in their optimal dose and schedule, and drug combinations should be given at consistent intervals. Because long intervals between cycles negatively affect dose intensity, the treatment-free interval between cycles should be the shortest possible time necessary for recovery of the most sensitive normal target tissue, which is usually the bone marrow. Finally, there should be a clear understanding of the biochemical, molecular, and pharmacokinetic mechanisms of interaction between the individual drugs in a given combination, to allow for maximal effect. Omission of a drug from a combination may allow overgrowth by a cell line sensitive to that drug alone and resistant to other drugs in the combination. Finally, arbitrary reduction in the dose of an effective drug to add other less effective drugs may dramatically reduce the dose of the most effective agent below the threshold of effectiveness and destroy the capacity of the combination to cure disease in a given patient.

Most standard treatment programs were designed around the kinetics of recovery of the bone marrow in response to chemotherapy exposure. The introduction of the colony-stimulating factors (CSFs), such as filgrastim and the long-acting molecule pegfilgrastim, has been a significant advance for cancer therapy, as they help to accelerate bone marrow recovery and prevent the onset of severe myelosuppression.[13] These cytokine growth factors have played an instrumental role in facilitating the delivery of dose-intense chemotherapy by reducing the incidence of infections and the need for hospitalizations. Without question, these agents have revolutionized the next generation of chemotherapy treatment.

No rigid schedule can accommodate all the variables assumed to be important for maximum effectiveness of combination chemotherapy. Physicians must often adjust doses at intervals to allow for the safe administration of drugs. The certainty that the therapeutic effect of a drug or drug combination can be lost if the dose or schedule is altered should temper these judgments. Reductions in dose rates also often result in only minimal decreases in toxicity but can lead to a major reduction in the capacity to attain a complete remission in patients with drug-responsive tumors.[14] The application of appropriate guidelines for dose reductions preserves the intervals between treatment cycles, pre-

serves the integrity of each drug combination and, finally, provides consistency between patients and various clinical studies.

For many years, clinical trial design was dominated by the use of alternating cycles of combination chemotherapy. The basis for this approach came from the translation of preclinical experimental data into a model for clinical treatment. In 1943, Luria and Delbruck[15] observed that the bacterium Escherichia coli developed resistance to bacterial viruses (bacteriophage) not by surviving exposure but by expanding clones of bacteria that had spontaneously mutated to a type inherently resistant to phage infection. This was a seminal principle in bacterial genetics that laid the framework for the understanding of the development of spontaneous resistance to cancer chemotherapy. In 1979, Goldie and Coldman[16] applied this principle to the development of resistance to anticancer drugs by cancer cells without prior exposure to these drugs. They proposed that the nonrandom cytogenetic changes now known to be associated with most human cancers probably were tightly associated with the development of the capacity to resist the action of certain types of anticancer drugs. They developed a mathematical model that predicted that tumor cells mutate to drug resistance at a rate intrinsic to the genetic instability of a particular tumor. Their model predicted that such events would begin to occur at population sizes between 10^3 and 10^6 tumor cells (1000 to 1 million cells), much lower than the mass of cells considered to be clinically detectable (10^9, or 1 billion cells). The probability that a given tumor will contain resistant clones when a patient's disease is newly diagnosed would be a function of both tumor size and the inherent mutation rate. If the mutation rate is as infrequent as 10^{-6}, a tumor composed of 10^9 cells (a 1-cm mass) would be predicted to have at least one drug-resistant clone; however, the absolute number of resistant cells in a tumor composed of 10^9 cells would be relatively small. Therefore, in the clinical setting, such tumors should initially respond to treatment with a partial or complete remission but would recur as the resistance clone expands to repopulate the tumor mass. Such a pattern is commonly seen in the clinical setting with the use of chemotherapy even in many drug-responsive tumors.

The Goldie-Coldman model predicts that cellular drug resistance should be present even with small tumors and that the maximal chance for cure occurs when all available effective drugs are given simultaneously. Because this would involve using multiple drugs, perhaps up to 8–10 drugs, administered simultaneously, this approach has not generally been tested in the clinic for fear that the use of more than five cytotoxic drugs, at full doses, would not be possible. An alternative approach, using two programs of equally effective, non–cross-resistant drug combinations in alternating cycles, has been under evaluation since the mid-1980s. However, many studies purporting to test the Goldie-Coldman hypothesis have not been properly designed. First, in many instances, inadequate testing has been carried out to determine whether the alternate combination is truly non–cross-resistant and is as effective as the primary treatment. In most instances, these requirements are not met. Second, except in rare instances, dosing is usually not controlled properly. Doses of es-

sential drugs are modified downward, a priori, without testing the potential impact of such dose reductions on outcome. Finally, the requirement for symmetry in biologic characteristics of tumors in different patients is unrealistic. The use of alternating cycles of combination chemotherapy has not yet proven to be more effective than full doses of a single effective combination program.

In the late 1980s, Norton and Day[17,18] reanalyzed the Goldie-Coldman hypothesis, and their mathematical model relaxed the requirement for symmetry. Although they confirmed the basic tenets of the Goldie-Coldman hypothesis, their model suggested a different approach to sequencing combinations. Their work suggested that the sequential use of combinations was predicted to outperform alternating cycles, because no two combinations were likely to be strictly non–cross-resistant or have equal cell-killing capacity, the symmetry assumed in the Goldie-Coldman model. There are now a growing list of clinical examples in which sequential therapies have outperformed alternating cyclic use of the same programs, when the dose intensity of the two regimens is carefully controlled.[19,20]

One final issue relating to chemotherapy relates to the optimal duration of drug administration. Several randomized trials in the adjuvant treatment of breast and colorectal cancer have generally shown that short-course treatment on the order of 6 months is as effective as long-course therapy (12 months).[21,22] While progressive disease during chemotherapy is a clear indication to stop treatment in the advanced disease setting, the optimal duration of chemotherapy for patients without disease progression has not been well-defined. With the development of novel and more potent drug regimens, the potential risk of cumulative adverse events, such as cardiotoxicity secondary to the anthracyclines and neurotoxicity secondary to the taxanes and the platinum analogs, must also be factored in the decision-making process. There is, however, no evidence of clinical benefit in continuing therapy indefinitely until disease progression. A recent randomized study in advanced colorectal cancer comparing continuous and intermittent palliative chemotherapy showed that a policy of stopping and re-challenging with the same chemotherapy provides a reasonable treatment option for patients.[23] Similar observations have been observed in the treatment of advanced, metastatic disease affecting other organ sites, including non-small cell lung cancer, breast cancer, germ cell cancer, ovarian cancer, and small cell lung cancer. However, for such an intermittent treatment approach to be adopted into clinical practice, several issues need to be addressed. First, the induction chemotherapy regimen must be of sufficient clinical efficacy and duration to ensure that the majority of responses are achieved during the treatment period. Second, there must be a good response to the reinitiation of the same chemotherapy or to the administration of an effective salvage chemotherapy regimen. Third, there should be a sufficient time interval between the termination of primary induction chemotherapy and the onset of progressive disease. Finally, patients who are taken off of active chemotherapy must be followed closely to ensure that treatment can be reinstituted at the first sign of disease progression.

The Concept of Dose Intensity

One of the main factors limiting the ability of chemotherapy and/or radiation therapy to achieve cure is effective dosing. The dose-response curve in biologic systems is usually sigmoidal in shape, with a threshold, a lag phase, a linear phase, and a plateau phase. For chemotherapy and radiation therapy, therapeutic selectivity is significantly dependent on the differential between the dose-response curves of normal and tumor tissues. In experimental in vivo models, the dose-response curve is usually steep in the linear phase, and a reduction in dose when the tumor is in the linear phase of the dose-response curve almost always results in a loss in the capacity to cure the tumor effectively before a reduction in the antitumor activity is observed. Thus, although complete remissions continue to be observed with dose reduction as low as 20%, residual tumor cells may not be entirely eliminated, thereby allowing for eventual relapse to occur. Although in vivo systems may not represent the ideal model for human malignancies, the general principles may be applicable to the clinical setting. Because anticancer drugs are associated with toxicity, it is often appealing for clinicians to avoid acute toxicity by simply reducing the dose or by increasing the time interval between each cycle of treatment. Such empiric modifications in dose represent a major reason for treatment failure in patients with drug-sensitive tumors who are receiving chemotherapy in either the adjuvant or advanced disease setting.

A major issue facing clinicians is the ability to deliver effective doses of chemotherapy in a dose-intense manner. The concept of dose intensity was put forth by Hryniuk et al.,[24,25] where they defined dose intensity to be the amount of drug delivered per unit of time. Specifically, this was expressed as milligrams per square meter per week, regardless of the schedule or route of administration. The dose intensity of each drug regimen is then determined based on the time period in which the treatment program is administered. Specific calculations can be made for the intended dose intensity, which is the dose intensity originally proposed in the treatment regimen, or the received dose intensity. It is the received dose intensity, rather than intended dose intensity, that is the more clinically relevant issue, as it reflects the direct impact of dose reductions and treatment delays imposed in actual practice. A positive relationship between dose intensity and response rate has been documented in several solid tumors, including advanced ovarian, breast, lung, and colon cancers, as well as in hematologic malignancies, including the lymphomas.

Calculations of the impact of dose intensity on outcome are particularly important in estimating the efficacy of adjuvant chemotherapy. The steep dose-response curve for most anticancer drugs indicates that dose reductions in adjuvant chemotherapy program are likely to be associated with significantly less therapeutic effect. Historically, dose reduction has been the common practice in the design of adjuvant trials. One example is the standard CMF regimen for breast cancer. The initial reports of this regimen revealed an impressive complete remission rate of approximately 30% in the advanced disease setting, albeit at the expense of considerable toxicity. When this regimen was advanced for use in the cooperative

group setting, initially for advanced disease and later for adjuvant trials by Bonadonna et al.,[26] the doses of the respective agents were arbitrarily reduced without first testing the potential impact of such reductions on clinical outcome. In addition, further reduction was empirically made for patients older than 60 years, with the assumption that such a dose reduction would be required for age. Careful analysis of the data suggest that such dose reductions have had a negative impact with respect to clinical outcome. The importance of dose effect was further confirmed by a large study in which a survival benefit was observed as a result of increasing dose intensity in the adjuvant chemotherapy for women with stage II, node-positive breast cancer.[27]

At present, there are three main approaches to deliver chemotherapy in a dose-intense fashion. The first approach is by dose escalation whereby the doses of the anticancer agents are increased. The second strategy is to administer anticancer agents in a dose-dense manner by reducing the interval between treatment cycles, while the third approach involves sequential scheduling of either single agents or of combination regimens. The use of a sequential scheduling should also be considered as a means to deliver chemotherapy in a dose-dense approach.

As has already been discussed in the section on "Cancer Cell Kinetics", the growth of most solid tumors follows a pattern of Gompertzian kinetics. In this setting, the growth of cells is significantly faster in the early part of the growth curve than at any other stage in the growth kinetics. For this reason, the initiation of chemotherapy at an earlier stage would be theoretically greater than at a later stage. The log cell kill generated by chemotherapy would, therefore, be greater in tumors of small volume than in those of large volume. In this setting, the regrowth of cancer cells between chemotherapy cycles is more rapid. Thus, the more frequent administration of cytotoxic chemotherapy would represent an attractive strategy to minimize residual tumor burden. In computer simulations, this relatively simple maneuver has, indeed, achieved significantly higher benefit by minimizing the regrowth of cancer cells between cycles of treatment. The clinical relevance of dose-density was recently supported by a landmark randomized phase III trial comparing dose-dense versus conventionally scheduled chemotherapy in the adjuvant therapy of node-positive primary breast cancer (INT C9741). Citron and colleagues[28] showed that a dose-dense schedule, in which the anticancer agents doxorubicin, cyclophosphamide, and paclitaxel were administered on an every-2-week schedule rather than at the conventional 3-week interval, resulted in significantly improved clinical outcomes with respect to DFS and OS. Of note, through concomitant use of the colony-stimulating factor filgrastim (G-CSF), dose-dense therapy was not accompanied by an increase in toxicity. While a dose-dense approach may have its greatest application in the adjuvant setting, there are growing examples where this strategy is also effective in the treatment of metastatic disease. Dose-dense regimens have shown superior clinical activity when compared to standard chemotherapy in metastatic colorectal cancer, extensive-stage small cell lung cancer, and poor-prognosis germ cell cancer.

One of the potential limitations of modern combination chemotherapy is that dose levels of individual drugs are usually reduced in an effort

to limit toxicity when used in combination. To address this issue, investigators have administered drug combinations in an alternating sequence to deliver a greater number of different drugs per unit time. This strategy, however, may not allow for enhanced dose intensity; in fact, it may actually compromise clinical benefit. A randomized clinical trial conducted by Bonadonna et al.[20] observed that four 3-week cycles of doxorubicin followed by eight 3-week cycles of CMF in women with high-risk primary breast cancer (four or more positive lymph nodes) was superior in terms of DFS and OS when compared to an alternating schedule of doxorubicin and CMF. Sledge et al.[29] addressed the issue of sequential versus combination therapy in the Eastern Cooperative Oncology Group E1193 randomized phase III trial of sequential single agent therapy with doxorubicin and paclitaxel versus the combination of the two agents in the first-line therapy of metastatic breast cancer. While combination therapy yielded a superior response rate and time to disease progression, this improvement in clinical benefit did not translate into a survival benefit when compared to sequential single-agent therapy. Moreover, combination therapy did not improve patient quality of life. Thus, this clinical study provides support to the notion that sequential chemotherapy represents a reasonable treatment option in patients with metastatic breast cancer. Such sequential strategies are being developed in other solid tumors, including colorectal cancer and ovarian cancer.

Apoptosis, Cell Cycle Control, and Resistance to Chemotherapy

The kinetic models described in the previous sections are relevant only in the context of a tumor that is sensitive to chemotherapy. For more than 30 years, the classic view of anticancer drug action has involved the specific interaction between a given drug and its respective target. Cell death arises as a direct consequence of this drug-receptor interaction. However, the critical molecular mechanisms involved in facilitating the initial coupling of the stimulus to the final response of the cell were never clearly elucidated. With an enhanced understanding of the molecular mechanisms underlying the control of the cell cycle and the process of programmed cell death (apoptosis), it is now clear that this simplistic model is insufficient to explain the cytotoxic effects of anticancer agents. In contrast to the drug-target interaction directly leading to cell death as was viewed in the classic model, it is now well-appreciated that such an interaction acts as the initial stimulus that then sets off a cascade of events eventually resulting in apoptosis. This pathway involves some type of sensor that detects a death-inducing signal, a signal transduction network, and an execution machinery that facilitates the process of cell death. Moreover, this entire process is exceedingly complex as it is highly dependent on the specific cell type under study, the specific anticancer agent being tested, and the cellular context and environment in which the drug-target interaction is being considered.

In addition, the capacity of certain cancers to resist the cytotoxic effects of cancer chemotherapy may be more closely connected to either

abnormalities in the genetic machinery of cancer cells or to alterations in the critical pathways of cell-cycle checkpoint control and apoptosis than to the specific mechanisms of resistance unique to each agent. This observation is underscored by the general failure to overcome resistance to chemotherapy in the clinic with approaches that attack only the classic biochemical or molecular mechanisms of resistance (or both). This section gives a brief overview of the complex interrelationship between products of cell-cycle checkpoint genes, oncogenic viruses, transcription factors, apoptosis, and chemotherapy as they relate to drug resistance, a more detailed discussion of these topics are reviewed elsewhere.

One of the remarkable features of both radiation therapy and chemotherapy is that their cytotoxic effects may be initially greater in neoplastic cells than in normal host tissues, including the bone marrow and the GI tract, when administered to sensitive tumors. Doses that eradicate some sensitive tumors will not ablate the bone marrow and/or destroy the capacity of the GI mucosa to regenerate. Until recently, there was no molecular basis for this therapeutic selectivity. Molecular genetic studies have revealed that, in contrast to malignant cells, normal cells such as those derived from the bone marrow and gut express an intact genetic machinery. As a result, the normal mechanisms for apoptosis and cell cycle arrest following exposure to genotoxic and cytotoxic stresses remain present. Thus, normal bone marrow and GI precursor cells are able to effectively monitor and repair DNA damage following exposure to a genotoxic stress as well as destroy cells with irreparable DNA, rather than allowing damaged cells to progress through the normal cell cycle and potentially replicate their damaged DNA. Because normal cells express an intact genetic machinery, they are able to recover from exposure to DNA-damaging anticancer agents, except in the case of high-dose chemotherapy, as observed in transplantation programs. In this setting, transplant doses of chemotherapy are able to overwhelm these protective mechanisms, resulting in direct cellular necrosis.

p53 is a tumor suppressor protein and critical transcriptional activator that plays a key role in mediating G_1 and G_2 arrest of the cell cycle following exposure to DNA-damaging agents and other genotoxic stress.[30,31] This function is thought to be essential in preserving the integrity of the cellular genome in response to treatment with a cytotoxic agent. In addition to its role in preserving the cell-cycle checkpoint, p53 is a potent inducer of programmed cell death (apoptosis) within a cell in which DNA damage has occurred. The basis for the cell's decision either to undergo growth arrest with subsequent repair of DNA damage or to induce apoptosis remains unclear. Significant research efforts are focused on elucidating the critical factors that determine the eventual cellular function of p53. This is undoubtedly a complex issue, that must take into account the extent of DNA damage, the stage of the cell cycle at which the DNA damage occurs, the presence of other genetic abnormalities in either the cell-cycle regulatory apparatus or the signaling machinery, the specific cellular environment within the cell, as well as exogenous factors contained within the cellular matrix. Of note, some tumor types, such as germ cell tumors and lymphomas have more rapid access to apoptotic mechanisms than the large majority of epithelial cancers.

Mutations in the p53 gene are among the most common genetic alterations observed in human tumor samples and have been estimated to occur in at least 50% of all human tumors.[32] The initial studies showing that loss of p53 function was associated with resistance to radiation therapy as well as chemotherapy came from in vivo model systems using p53 knockout mice.[33,34] Subsequent studies have confirmed that various malignant cell lines and tumors expressing mutant or deleted p53 are chemoresistant to a wide range of anticancer agents. However, loss of p53 function is not always associated with chemoresistance. Some studies suggest that cells with impaired p53 function can become sensitized to various anticancer agents. Thus, the relationship between p53 status and chemosensitivity is complex and is presumably dependent on a number of factors, including the specific cytotoxic stimuli, tissue-specific differences, and the specific cellular context that incorporates the overall genetic machinery and the various intracellular signaling pathways.

The specific cytotoxic treatment, the conditions of treatment, p53 status, and other cell-cycle regulatory elements may all contribute to the outcome of an exposure of a cell to DNA-damaging agents. If the dose of the treatment is exceedingly high, non-apoptotic cell death (e.g., necrotic cell death due to DNA or other damage) may occur. At an intermediate level of dose intensity, p53-dependent or p53-independent apoptotic cell death can occur. When p53 function is intact, the level of inhibitors of p53 is not high, and the regulatory environment of the cell is such that the cell circumvents the interruption of the cell-cycle progression that occurs after DNA damage, the cell will undergo p53-dependent apoptosis. However, in the setting of abnormal p53 function, whether through the acquisition of point mutations in the p53 gene, posttranslation inactivation of p53 through binding to other protein partners (e.g., MDM2) or enhancement of the degradation (e.g., the E6 protein of the human papilloma virus), or decreased translation of wild-type p53 messenger RNA by the folate-dependent enzyme thymidylate synthase, the cell is unable to undergo cell-cycle arrest or apoptosis in response to DNA damage. In a tumor population, the functional inactivation of p53 through any of these regulatory mechanisms facilitates genomic instability and contributes to the development of cellular resistance. Normal hematopoietic and GI mucosa cells are genetically stable as a result of an intact p53 mechanism that provides them with the ability to undergo apoptosis following treatment with chemotherapy.

It is conceivable that increasing growth rates may be associated with increasing levels of drug resistance through the increased transcription of genes involved in rapid cell growth and entry into the cell cycle. The high degree of resistance in more advanced tumors, including the spontaneous development of resistance, which was the basis of the Goldie-Coldman hypothesis, and the development of multidrug resistance, appears more likely to be related to mutations in key genes in the cell-cycle regulatory system than to drug-specific spontaneous mutations, as was proposed in the past. Cell death in response to exposure to DNA-damaging agents may require an intact p53-dependent apoptotic mechanism under some experimental circumstances. However, it also

may depend on the activation of alternative pathways of apoptosis or some degree of reregulation of the system that would ultimately lead to the reduced release of transcription factors from genes such as RB, or a homologous gene, p107, and the production of lower levels of growth-related gene products, thereby sensitizing cells to chemotherapeutic agents. An enhanced understanding of the complexities surrounding chemotherapy-induced cell death may shed new insights that would have profound implications for the design of future approaches to therapy that might couple standard cytotoxic agents to new biologic agents that attack specific molecular targets to reregulate the cell-cycle checkpoint.

Because apoptosis is a genetically programmed event, inactivation of genes that induce the apoptotic program or activation of antiapoptotic genes can result in the development of cellular drug resistance. Bcl-2 is a potent suppressor of apoptotic cell death, and a number of studies have shown that its expression leads to repression of cell death triggered by either γ-irradiation or a variety of anticancer agents.[35,36] In addition, the phosphorylation status of Bcl-2 may play an important role as a determinant of chemosensitivity.[37] There is growing evidence that the phosphorylated form of Bcl-2 interacts less efficiently with its heterodimer protein partner bax, resulting in cell death. Bcl-x_L, a functional and structural homologue of Bcl-2, is also able to confer protection against radiation induced apoptosis as well as against a wide number of anticancer agents, including bleomycin, cisplatin, etoposide, and vincristine.

The molecular mechanisms and intracellular signal transduction pathways initiated by a given cytotoxic and/or genotoxic stress may differ significantly. However, the final stage of these various death pathways is mediated through the activation of caspases,[38,39] which represent a highly conserved family of cysteine proteases. The activation of caspases is determined by the intrinsic and extrinsic pathways of apoptosis. The intrinsic pathway is a mitochondrial-dependent pathway mediated by the Bcl-2 family of proteins. Exposure to cytotoxic stress results in disruption of the mitochondrial membrane which then leads to release of cytochrome c and other protease activators. Caspase-9 is subsequently activated, setting off a cascade of events that commits the cell to undergo apoptosis. The extrinsic pathway is mediated by ligand binding to the tumor necrosis factor family of receptors (TNFR), which includes TNF R1, Fas, DR3, DR4 (tumor necrosis factor-related apoptosis-inducing ligand [TRAIL] R1), DR5 (TRAILR2) or DR6, coupled with an intracytoplasmic death domain protein and certain essential adaptor proteins. These adaptor proteins recruit various proteases and then cleave the N-terminal domain of caspase-8, which leads to activation of the caspase cascade.

The presence of several external stimuli, including various cytokines, tumor necrosis factor-α (TNF-α), chemotherapy, and radiation, leads to activation of the transcription factor NF-κB.[40] Paradoxically, activation of NF-κB results in potent suppression of the apoptotic potential of these stimuli. Several studies have demonstrated that inhibition of NF-κB in vitro leads to enhanced apoptosis in response to different stimuli.[41] Chemoresistant fibrosarcoma tumors derived from HT1080 cells become resensitized to the apoptotic potential of TNF-α and the topoisomerase I

compound, irinotecan, leading to significant antitumor activity. These findings suggest that activation of NF-κB expression in response to chemotherapy may represent an important mechanism of inducible tumor chemoresistance. Moreover, they suggest that strategies to inhibit NF-κB may represent a rational approach to enhance and/or chemosensitivity to antitumor therapy through increased apoptosis, and such an approach is discussed in the next section.

Development of Novel Therapeutic Strategies

A wide range of signal transduction pathways have been identified as critical for the growth and proliferation of individual tumors. There is also growing evidence that many of these signaling pathways are intimately involved with other key cellular events including DNA repair, cell survival signals, invasion/metastasis, and the process of angiogenesis. Moreover, many of these same signaling pathways may play a key role in mediating sensitivity to chemotherapy and/or radiation therapy. Significant efforts are now focused on translating this knowledge for the rational design and development of novel therapeutic approaches to improve the efficacy of chemotherapy.

The agent that ushered in this new era of targeted therapies is the small molecule inhibitor imatinib. This anticancer agent was rationally designed based upon the crystal structure of the Bcr-Abl tyrosine kinase, which is expressed solely in chronic myeloid leukemia (CML). This molecule binds to the ATP pocket within the enzyme. In addition, imatinib inhibits other related tyrosine kinases, including platelet-derived growth factor (PDGF), stem cell factor (SCF), and c-kit. In so doing, imatinib functions as a potent competitive inhibitor of ATP binding, and inhibits substrate phosphorylation and downstream signaling pathways. This agent is currently approved for the treatment of chronic myeloid leukemia (CML).[42] Of note, given its high level of specificity for CML, this agent has a favorable safety profile, and its associated side effects are usually mild. In addition to CML, treatment with imatinib is curative in patients with refractory gastrointestinal stromal tumors that express the c-kit tyrosine kinase.[43]

The epidermal growth factor receptor (EGFR) signaling pathway is presently one of the most actively investigated areas of cancer drug development.[44] Preclinical studies have shown that activation of EGFR and its downstream signaling events plays a key role in regulating tumor cell growth and proliferation, DNA repair and survival, invasion/metastasis, and angiogenesis. Second, increased expression of EGFR is observed in a broad range of solid tumors, including colorectal cancer, non-small cell lung cancer, head and neck cancer, pancreatic cancer, and breast cancer. Finally, a number of clinical studies have correlated expression of EGFR with disease progression, poor treatment outcome, and poor patient survival. Several approaches have been developed to inhibit the EGFR pathway, and they include small molecule inhibitors of the tyrosine kinase (TKI) domain of the receptor, monoclonal antibodies directed against

the cell surface receptor, and antisense molecules directed against the mRNA encoding the EGFR-associated tyrosine kinase. The first two strategies have been tested in the clinical setting, and there is evidence that both TKIs and monoclonal antibodies have clinical activity. Gefitinib and erlotinib are oral, highly selective, reversible inhibitors of the tyrosine kinase domain associated with the EGFR, and both agents are approved as monotherapy by the FDA for the treatment of patients with locally advanced or metastatic NSCLC after failure of prior chemotherapy. With respect to antibody-directed therapy, there are three monoclonal antibodies currently being investigated, cetuximab (IMC-C225), matuzimab (EMD72000), and panitumomab (ABX-EGF). The chimeric IgG_1 antibody cetuximab is furthest along in clinical development, and is presently approved for use in the treatment of metastatic colorectal cancer that is refractory to irinotecan-based chemotherapy. As monotherapy, cetuximab has clinical activity with a 10–12% response rate in heavily pretreated patients with advanced colorectal cancer. Perhaps of greater significance is that treatment of irinotecan-resistant patients with advanced colorectal cancer with cetuximab in combination with the topoisomerase I inhibitor irinotecan is able to restore sensitivity to irinotecan therapy, yielding overall response rates in the 21–23% range.[45]

A critical determinant for a cancer cell to undergo apoptosis or cell cycle arrest with repair of DNA damage may be the presence or absence of essential growth factors within the cellular environment. Thus, in the absence of growth factor stimuli, the cell would become committed to the apoptotic pathway following exposure to a cytotoxic stress. Both preclinical and clinical studies suggest that this scenario may indeed be true. The positive clinical results with the anti-EGFR antibody cetuximab in combination with irinotecan certainly provide support to this concept. A similar enhancement has been observed when the anti-HER2-neu monoclonal antibody (trastuzumab), a member of the erbB family and closely related to the anti-EGFR antibodies, is used in combination with either paclitaxel or the combination of cyclophosphamide and doxorubicin for the treatment of advanced breast cancer.[46] While this antibody has single-agent activity in Her2-neu-expressing breast cancer, significantly higher activity is observed when it is used in combination with chemotherapy, and this agent is currently approved by the Food and Drug Administration for both monotherapy and combination treatment of advanced breast cancer.

The vascular endothelial growth factor (VEGF) is one of the most critical angiogenic growth factors known to regulate the process of angiogenesis. The growth of both primary and metastatic tumors requires an intact vasculature; for this reason, VEGF and the VEGF-signaling pathway represent an attractive target for chemotherapy.[47] Several approaches have been taken to inhibit VEGF signaling, and they include inhibition of VEGF/VEGF receptor interactions by targeting either the VEGF ligand with antibodies or soluble chimeric receptors or by direct inhibition of the VEGF receptor–associated tyrosine kinase activity by small molecule inhibitors.

Bevacizumab is a recombinant humanized monoclonal antibody that targets all forms of VEGF-A. This antibody binds to and prevents VEGF-A

from interacting with the target VEGF receptors. A series of clinical studies have now shown that bevacizumab significantly enhances the clinical efficacy of 5-FU-, oxaliplatin-, and irinotecan-based chemotherapy in patients with metastatic colorectal cancer, and for this reason, this antibody is approved for use as first-line treatment for metastatic colorectal cancer in combination with any intravenous fluoropyrimidine-containing regimen.[48]

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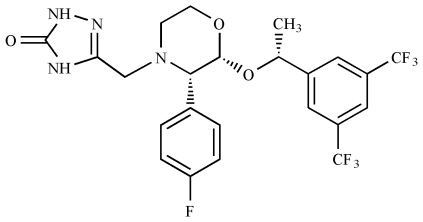
5

Antiemetic Agents for the Treatment of Chemotherapy-Induced Nausea and Vomiting

M. Sitki Copur, Laurie J. Harrold, Richard Kim, and Edward Chu

This chapter presents an overview of the common antiemetic agents as well as selected regimens for the treatment of chemotherapy-induced nausea and vomiting. The specific agents are organized alphabetically, and the various regimens selected are used in clinical practice in the medical oncology community. It should be emphasized that not all of the drugs and dosages in the regimens have been officially approved by the Food and Drug Administration (FDA). This chapter should serve as a quick reference for physicians and healthcare providers and provides several options for treating both acute and delayed nausea and vomiting. It is not intended to be an all-inclusive review of antiemetic agents and treatment regimens, and neither is it intended to endorse and/or prioritize any particular drug or regimen.

Aprepitant



Trade Name

Emend

Classification

Substance P/NK1 receptor antagonist

Category

Antiemetic agent

Drug Manufacturer

Merck

Mechanism of Action

- Selective high-affinity antagonist of substance P/neurokinin 1 (NK1) receptors.
- Inhibits the acute and delayed phases of chemotherapy-induced emesis.
- Little to no affinity for 5-HT_3, dopamine, or corticosteroid receptors.

Absorption

Well absorbed by the GI tract, and oral bioavailability is on the order of 60%–65%. Peak plasma levels reached in 4 hours. Ingestion of food does not alter the extent of absorption.

Distribution

Crosses the blood-brain barrier and enters the central nervous system (CNS). Greater than 95% of drug is bound to plasma proteins.

Metabolism

Undergoes extensive metabolism in the liver, principally by the CYP3A4 liver microsomal system. The main route of elimination of parent drug is via liver metabolism. The drug and its metabolites are not renally excreted. The elimination half-life ranges from 9–13 hours.

Indications

Prevention of acute and delayed nausea and vomiting associated with highly emetogenic cancer chemotherapy.

Dosage Range

Oral: Recommended dose is 125 mg PO given one hour before chemotherapy and 80 mg PO on days 2 and 3 after chemotherapy.

Drug Preparation

Available as 80 and 125 mg capsules.

Drug Interaction 1

Inhibitors of CYP3A4 liver microsomal activity—Aprepitant is a substrate for CYP3A4, and increased plasma levels of aprepitant may be observed in the presence of CYP3A4 inhibitors, including ketoconazole, itraconazole, clarithromycin, ritonavir, nelfinavir, nefazodone, and troleandomycin.

Drug Interaction 2

Inducers of CYP3A4 liver microsomal activity—Aprepitant is a substrate for CYP3A4, and reduced plasma levels may be observed in the presence of CYP3A4 inducers, including rifampin, carbamazepine, and phenytoin.

Drug Interaction 3

Warfarin—Coadministration of aprepitant with warfarin may result in a decrease in coagulation parameters, PT/INR.

Special Considerations

1. Use with caution in patients on chronic warfarin anticoagulation. Coagulation parameters, PT/INR, should be closely monitored in the 2-week period, especially at days 7 and 10, following aprepitant therapy.
2. Patients should be advised to report to their physician the use of any non-prescription or herbal medications, as significant drug interactions can occur with aprepitant and other drugs.
3. Well-tolerated in patients with mild to moderate liver dysfunction. Caution should be exercised in patients with severe hepatic insufficiency (Child-Pugh score > 9).
4. No dose adjustment is required for patients with renal insufficiency and/or those undergoing hemodialysis.
5. Pregnancy category B. Breast-feeding should be avoided.

Toxicity 1

Fatigue is most common side effect. CNS effects include headache and insomnia.

Toxicity 2

GI side effects include constipation and/or diarrhea.

Toxicity 3

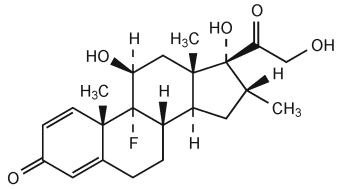
Hiccups observed in 10% of patients.

Toxicity 4

Anorexia.

D

Dexamethasone



Trade Name

Decadron

Classification

Glucocorticoid steroid

Category

Antiemetic agent

Drug Manufacturer

Merck

Mechanism of Action

- Precise mechanism of action in preventing and/or treating cancer chemotherapy-induced nausea and vomiting is not known.
- Suppresses prostaglandin release from hypothalamus, which may then inhibit the subsequent process of nausea and vomiting.
- Possesses anti-inflammatory and immunosuppressive effects with minimal mineralocorticoid properties.

Absorption

Well absorbed by the gastrointestinal (GI) tract, and oral bioavailability is on the order of 60%–70%. Peak plasma levels are observed in 1–2 hours after doses of 0.5–3.0 mg and are independent of the route of administration.

Distribution

Dexamethasone binds corticosteroid-binding globulin and corticosteroid-binding albumin to significantly less extent than does hydrocortisone.

Metabolism

Metabolism occurs primarily in the liver, and about 20% of the drug is conjugated to the glucuronide metabolite. The main route of elimination is through renal excretion with biliary excretion playing a minor role. The elimination half-life is 3–4 hours.

D

Indications

Treatment of nausea and vomiting associated with cancer chemotherapy in combination with other antiemetics, including serotonin (5-HT_3) receptor antagonists, metoclopramide, and lorazepam.

Dosage Range

1. The optimum dosage of dexamethasone for the prevention and/or treatment of cancer chemotherapy-induced nausea and vomiting has not been established.
2. Oral: Recommended dose is 4 mg PO every 4–6 hours for 4 doses with first dose given 1–6 hours before chemotherapy.
3. Intravenous (IV): Recommended dose is 10–20 mg IV before chemotherapy and then 10–20 mg IV every 4–6 hours.

Drug Preparation

- Available as 0.25, 0.5, 0.75, 4, and 6 mg pentagonal-shaped tablets or as a clear red elixir form (0.5 mg/mL) for oral use.
- Available as 4 mg/mL or 24 mg/mL injectable vials for IV use.

Drug Interaction 1

Inducers of liver microsomal P450 system—Phenytoin, phenobarbital, carbamazepine, ephedrine, and rifampin may induce the liver microsomal system and thus enhance the metabolism of dexamethasone.

Drug Interaction 2

Aspirin, nonsteroidal agents—Increased GI irritation and bleeding may be observed with concurrent administration of dexamethasone and aspirin and/or nonsteroidal agents.

Special Considerations

1. Contraindicated in patients with an underlying psychiatric disorder, including psychosis and depression.
2. Efficacy of dexamethasone may be decreased when used in the presence of drugs that induce the liver microsomal P450 system, including phenytoin, phenobarbital, and carbamazepine. In this setting, the dose of drug may need to be increased.
3. Use with caution in patients with liver impairment and/or hypothyroidism as increased drug effects may be observed.
4. Patients should be cautioned about possible neuropsychiatric side effects, including mood changes, euphoria, depression, insomnia, and in extreme cases, psychosis.

Toxicity 1

Electrolyte abnormalities with hypokalemia and hyperglycemia.

Toxicity 2

Fluid retention, leg edema, hypertension, and rarely, exacerbation of congestive heart failure (CHF).

Toxicity 3

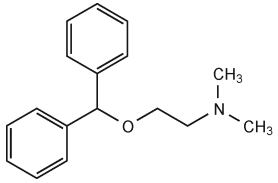
Neuropsychiatric effects, including mood changes, euphoria, headache, insomnia, depression, and psychosis.

Toxicity 4

Increased white blood count (WBC) secondary to demargination.

Diphenhydramine

D



Trade Name

Benadryl

Classification

Antihistamine

Category

Antiemetic agent

Drug Manufacturer

Parke-Davis

Mechanism of Action

- Antihistamine with anticholinergic and sedative effects. Competes with histamine for receptor sites on effector cells.
- Blocks the chemoreceptor trigger zone and decreases vestibular stimulation.

Absorption

Well absorbed by the GI tract, and oral bioavailability is on the order of 40%–60%. Peak plasma levels reached in 1–4 hours.

Distribution

Widely distributed throughout the body, including the central nervous system (CNS). Crosses the placenta and is excreted in breast milk. About 80%–85% of drug is bound to plasma proteins.

Metabolism

Metabolism occurs in the liver, principally to diphenylmetoxyacetic acid, which may then undergo conjugation. The main route of elimination of parent drug and its metabolites is through renal excretion. The elimination half-life ranges from 2.5–9 hours.

Indications

1. Prevention of nausea and vomiting associated with cancer chemotherapy in combination with other antiemetics, including 5-HT_3 receptor antagonists, metoclopramide, and lorazepam.
2. Active treatment of motion sickness.
3. Prevention and/or treatment of allergic, hypersensitivity reactions.
4. Temporary relief of cough caused by minor irritation of upper airways.
5. Treatment of parkinsonism.

Dosage Range

1. Oral: Recommended dose is 25–50 mg PO before chemotherapy and then every 4–6 hours thereafter.
2. IV: Recommended dose is 10–50 mg IV before chemotherapy.

Drug Preparation

- Available as 25 and 50 mg capsules; 12.5 mg/5 mL elixir solution; and 25 and 50 mg film-coated tablets for oral use.
- Available as 10 and 50 mg/mL injectable vials for IV use.

Drug Interaction 1

Alcohol and CNS depressants—Diphenhydramine has additive effects with alcohol and other CNS depressants, including sedatives, hypnotics, and tranquilizers.

Drug Interaction 2

Monoamine oxidase (MAO) inhibitors—Anticholinergic effect of diphenhydramine is prolonged and enhanced with concomitant use of MAO inhibitors.

Special Considerations

1. Use with caution in patients with a history of increased intraocular pressure, narrow-angle glaucoma, bladder-neck obstruction, bronchial asthma, cardiovascular disease, and/or hypertension.
2. Use with caution in elderly patients as they are more likely to exhibit altered sensorium with drowsiness and confusion.
3. Patients should be advised against performing activities that require mental alertness, including operating heavy machinery and driving.
4. Useful to treat and/or prevent extrapyramidal side effects related to antiemetic therapy.
5. Pregnancy category B. Breast-feeding should be avoided.

Toxicity 1

CNS effects are most commonly observed with sedation, drowsiness, dizziness, and confusion. Alterations in coordination, irritability, and insomnia.

Toxicity 2

Dryness of mucous membranes, including mouth, nose, and throat.

Toxicity 3

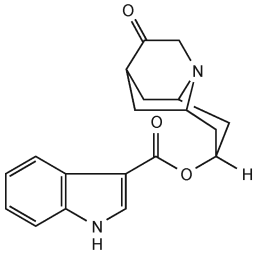
Hypotension, palpitations, and tachycardia.

Toxicity 4

Anorexia.

D

Dolasetron



Trade Name

Anzemet

Classification

5-HT_3 receptor antagonist

Category

Antiemetic agent

Drug Manufacturer

Aventis

Mechanism of Action

- Competitive, highly selective antagonist of type 3, 5-HT_3 receptors.
- 5-HT_3 receptors are present centrally, in the chemoreceptor trigger zone of the area postrema of brain, and peripherally, on vagal nerve terminals. Antiemetic action of dolasetron may be mediated centrally, peripherally, or at both sites.
- Does not have direct dopamine-receptor antagonist activity.
- Effective in acute nausea and vomiting but plays only a limited role in delayed emesis.

Absorption

Well absorbed by the GI tract. Oral bioavailability is approximately 75%. Food does not affect oral absorption.

Distribution

Widely distributed in the body. Approximately 70%–80% of drug is bound to plasma proteins.

Metabolism

Parent drug is rarely detected in plasma due to rapid and complete metabolism to hydrodolasetron, which is further metabolized in the liver by the cytochrome P450 microsomal system. Main routes of metabolism include hydroxylation and glucuronidation. Hydrodolasetron is eliminated by both renal and hepatic excretion, with about 60% of an administered dose recovered in the urine and 30% in the feces. The mean elimination half-life in adult cancer patients is approximately 8 hours.

Indications

1. Prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.
2. Prevention of postoperative nausea and vomiting.

Dosage Range

1. Oral: Recommended dose is 100 mg PO once daily given 1 hour before chemotherapy.
2. For the prevention of postoperative nausea and vomiting, 100 mg PO within 2 hours before surgery.
3. IV: Recommended dose is 1.8 mg/kg IV as a single dose administered 30 minutes before chemotherapy. As an alternative, a fixed dose of 100 mg IV can be administered 30 minutes before chemotherapy.

Drug Preparation

- Available as 50 and 100 mg pink, film-coated tablets for oral use.
- Available as a 20 mg/mL solution in 0.625 mL single-use ampules or 5 mL single-use vials for IV use. Stock solution should be protected from light and kept at room temperature.
- Dolasetron injection may be administered intravenously either undiluted over 30 seconds or diluted with 0.9% sodium chloride or 5% dextrose and infused over 15 minutes.
- Diluted solution is stable for 24 hours at room temperature and for 48 hours upon refrigeration.

Drug Interaction 1

Inducers of hepatic cytochrome P450 enzymes—Inducers of the liver P450 system, such as rifampin, may decrease the blood levels of hydrodolasetron.

Drug Interaction 2

Inhibitors of hepatic cytochrome P450 enzymes—Inhibitors of the liver P450 system, such as cimetidine, may increase the blood levels of hydrodolasetron.

Special Considerations

1. No dose adjustment is required in elderly patients or in those with hepatic and/or renal impairment.
2. Use with caution in patients who have or may develop cardiac conduction abnormalities, including those with prolonged PR and QT intervals. Baseline electrocardiograms should be performed before administration of dolasetron and chemotherapy.
3. Use with caution in patients who are receiving antiarrhythmic agents or other drugs that can prolong the PR, QRS, and QT intervals.
4. Careful monitoring of electrolytes, including potassium and magnesium, is required to reduce the occurrence of arrhythmias.
5. Pregnancy category B. Breast-feeding should be avoided.

Toxicity 1

Headache is most common side effect (18%–25%).

Toxicity 2

Diarrhea and/or abdominal pain.

Toxicity 3

Fever, fatigue, and dizziness.

Toxicity 4

Hypotension, chest pain, orthostatic hypotension, syncope, bradycardia and Mobitz I atrioventricular (AV) block, and atrial arrhythmias, including atrial flutter and atrial fibrillation.

Toxicity 5

Agitation, sleep disorder, confusion, depersonalization, anxiety, and abnormal dreams.

Toxicity 6

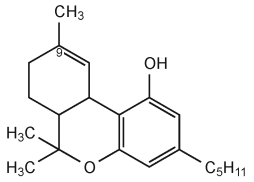
Transient elevations in liver function tests (LFTs). Usually clinically asymptomatic.

Toxicity 7

Hypersensitivity reactions with dyspnea, skin rash, urticaria, bronchospasm, and hypotension have been reported in rare instances.

Dronabinol

D



Trade Name

Marinol

Classification

Cannabinoid

Category

Antiemetic agent

Drug Manufacturer

Roxane and Unimed

Mechanism of Action

- Precise mechanism of action in preventing and/or treating cancer chemotherapy-induced nausea and vomiting is not known.
- Complex effects on the CNS with central sympathomimetic activity.
- Binding to cannabinoid receptors in CNS may contribute to its antiemetic effect.
- Inhibition of vomiting control mechanism in the medulla oblongata.

Absorption

Nearly completely absorbed (90%–95%) by the GI tract. Onset of action occurs within 0.5–1 hours after ingestion. Peak plasma levels are observed in 2–4 hours with 3–6 hours duration of action.

Distribution

Because of extensive first-pass metabolism in the liver, only 10% of an administered dose reaches the systemic circulation. Highly bound to plasma proteins (97%).

Metabolism

Undergoes extensive first-pass metabolism in the liver microsomal system. Both active and inactive metabolites are formed. The main active metabolite is 11-hydroxy-delta tetrahydrocannabinol (THC). Dronabinol and the 11-hydroxy metabolite are present in nearly equal concentrations in plasma. The main route of elimination is via biliary excretion. The elimination half-life of the parent drug is 25–36 hours, while that of the 11-hydroxy metabolite is 15–18 hours.

Indications

1. Treatment of nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond to conventional antiemetic agents.
2. Stimulates appetite and prevents weight loss in patients with AIDS.

Dosage Range

Recommended dose is 5–15 mg/m^2 PO 1–3 hours before chemotherapy and then every 4–6 hours PO thereafter.

Drug Preparation

- Available as 2.5, 5, and 10 mg gelatin capsules for oral use.
- Available as 5 to 25 mL injectable vials for IV use.

Drug Interactions

Sedatives, hypnotics, psychoactive agents—Avoid concurrent use of dronabinol with these drugs as there may be increased incidence of sedation.

Special Considerations

1. Use with caution in elderly patients due to an increased risk of neuropsychoactive effects.
2. Use with caution in patients with a history of alcohol and/or substance abuse.
3. Prescriptions should be limited to only one course of chemotherapy.
4. Use with caution in patients with underlying psychiatric disorders, including mania, depression, or schizophrenia.
5. Patients should be cautioned about possible neuropsychiatric side effects, including mood changes, euphoria, depression, insomnia, and in extreme cases, psychosis.
6. Pregnancy category C.

Toxicity 1

Mood changes, drowsiness, confusion, and dizziness. Impairment in perception, coordination, and sensory function. Visual distortions, nightmares, hallucinations, and depersonalization are also observed.

Toxicity 2

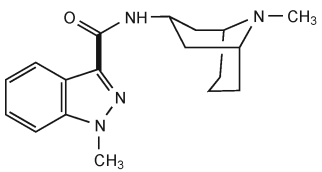
Orthostatic hypotension, tachycardia, facial flush, conjunctival injection, and palpitations.

Toxicity 3

Dry mouth, abdominal pain, and diarrhea occur in less than 10% of patients.

G

Granisetron



Trade Name

Kytril

Classification

5-HT_3 receptor antagonist

Category

Antiemetic agent

Drug Manufacturer

Roche

Mechanism of Action

- Competitive, highly selective antagonist of type 3, 5-HT receptors.
- 5-HT_3 receptors are present centrally, in the chemoreceptor trigger zone of the area postrema of brain, and peripherally, on vagal nerve terminals. Antiemetic action of granisetron may be mediated centrally, peripherally, or at both sites.
- Does not have direct dopamine-receptor antagonist activity.
- Effective in preventing acute chemotherapy-induced nausea and vomiting.

Absorption

Well absorbed by the GI tract. Mean bioavailability ranges from 48% to 75%. Absorption is decreased in the presence of food.

Distribution

Distributes freely between plasma and red blood cells. Approximately 65% of drug is bound by plasma proteins.

Metabolism

Undergoes extensive metabolism in the liver by the cytochrome P450 microsomal system. Main routes of metabolism include N-demethylation and oxidation followed by conjugation. Some of the metabolites may have 5-HT_3 antagonist activity. About 12% of an administered dose is recovered as the parent compound in the urine. The mean elimination half-life in adult cancer patients is approximately 9 hours.

Indications

1. Prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin.
2. Prevention of nausea and vomiting associated with radiation, including total body irradiation and fractionated abdominal radiation. (Oral solution and tablets only.)

Dosage Range

1. Oral: Recommended dose is 2 mg PO once daily given 1 hour before chemotherapy. An alternative regimen is 1 mg PO bid with the first 1 mg dose given 1 hour before chemotherapy and the second dose given 12 hours after the first dose.
2. For the prevention of radiotherapy-induced nausea and vomiting, 2 mg PO once daily to be taken within 1 hour of radiation therapy.
3. IV: Recommended dose is 10 μg/kg IV administered 30 minutes before chemotherapy.

Drug Preparation

- Available as a 1 mg white, film-coated tablet for oral use.
- Available as a 1 mg/mL solution in 1 mL single-dose or 4 mL multidose vials for IV use. Stock solution should be protected from light and should **NOT** be frozen.
- Available as an oral solution at 2 mg/10 mL in a 30 mL bottle.
- Granisetron injection may be administered intravenously either undiluted over 30 seconds or diluted with 0.9% sodium chloride or 5% dextrose and infused over 5 minutes.
- Available as a 0.1 mg/1 mL solution in 1 mL single-use vial for IV use in pediatric patients.

Drug Interaction 1

Inducers of hepatic cytochrome P450 enzymes—Inducers of the liver P450 system, including alcohol, barbiturates, carbamazepine, efavirenz, griseofulvin, modafinil, nevirapine, phenylbutazone, phenytoin, rifabutin, rifampin, and rifapentine, may change the clearance and the half-life of granisetron. No dosage adjustment is recommended, but caution is recommended when any of these drugs are taken concurrently with granisetron.

Drug Interaction 2

Inhibitors of hepatic cytochrome P450 enzymes—Inhibitors of the liver P450 system, including allopurinol, amiodarone, amprenavir, MAO inhibitors, isoniazid, phenylbutazone, omeprazole, valproic acid, and verapamil, may change the clearance and half-life of granisetron. No dosage adjustment is recommended, but caution is recommended when any of these drugs are taken concurrently with granisetron.

Special Considerations

1. No dose adjustment is required in elderly patients or in those with hepatic and/or renal impairment.
2. There appears to be little difference in clinical efficacy between oral dosing of 1 mg bid or a single daily dose of 2 mg.
3. Granisetron is especially effective when combined with dexamethasone in treating cisplatin-associated nausea and vomiting.
4. Granisetron does not induce or inhibit the liver microsomal P450 system.
5. Granisetron can be administered by IV in pediatric patients ages 2–16.
6. Pregnancy category B. It is not known whether granisetron is excreted in human milk. Caution should be exercised when Kytril is administered to a nursing woman.

Toxicity 1

Headache is the most common side effect (15%–20%).

Toxicity 2

Constipation, diarrhea, and/or abdominal pain.

Toxicity 3

Asthenia.

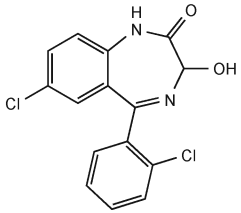
Toxicity 4

Transient elevations in LFTs. Usually clinically asymptomatic.

Toxicity 5

Hypersensitivity reactions with dyspnea, skin rash, urticaria, bronchospasm, and hypotension have been reported in rare instances.

Lorazepam



Trade Name

Ativan

Classification

Benzodiazepine

Category

Antiemetic agent

Drug Manufacturer

Elkins-Sinn and Watson

Mechanism of Action

- Interacts with the γ-aminobutyric acid (GABA)-benzodiazepine receptor complex, which is widely expressed in the brain.
- Exhibits relatively high affinity for GABA recognition site and enhances the binding affinity of GABA for its receptor site on the same receptor complex.
- Intensity of action, including antianxiety effects, sedation, and reduction of seizure activity, appears to be directly related to the occupancy status of the receptor.

Absorption

Well absorbed by the GI tract with an oral bioavailability of nearly 90%. Peak concentrations in plasma occur approximately 2 hours following oral or intramuscular (IM) administration. Absorption after IM injection is rapid and complete.

Distribution

Widely distributed in body tissues and crosses the blood-brain barrier. Lorazepam and its metabolites cross the placenta and are distributed into milk. Approximately 90% of parent drug and its metabolites are bound to plasma proteins.

Metabolism

Undergoes extensive conjugation in the liver to the glucuronide metabolite, which is then excreted mainly into the urine. The mean half-lives of unconjugated lorazepam and its major metabolite, lorazepam glucuronide, are 12 and 18 hours, respectively.

Indications

1. Management of nausea and vomiting associated with emetogenic cancer chemotherapy either alone or in combination with other drugs, such as 5-HT_3 receptor antagonists and/or corticosteroids.
2. Management of anxiety disorders and acute relief of symptoms of anxiety and/or anxiety associated with depressive symptoms.
3. Management of preoperative anxiety.
4. Management of status epilepticus.

Dosage Range

1. Dosage of lorazepam must be individualized, and the smallest effective dose should be used, especially in those with low serum albumin.
2. Recommended oral dose as an antiemetic agent is 2.5 mg of lorazepam PO on the evening before and just after initiation of chemotherapy.
3. Recommended IV dose is 1.5 mg/m^2 (maximum, 3 mg) IV administered 45 minutes before the initiation of chemotherapy.

Drug Preparation

Available as 0.5, 1, and 2 mg white tablets for oral use or in vials of 2 or 4 mg/mL for IV use.

Drug Interaction 1

CNS depressants (alcohol, phenothiazines, barbiturates, MAO inhibitors, scopolamine, loxapine, clozapine, haloperidol)—Administration of lorazepam may worsen depression of CNS when administered with other CNS depressants.

Drug Interaction 2

Valproic acid—Concurrent administration of lorazepam with valproic acid results in decreased formation of lorazepam glucuronide and decreased total clearance of lorazepam.

Drug Interaction 3

Oral contraceptives—Concurrent administration of lorazepam with oral contraceptives results in an increase in total clearance of lorazepam.

Drug Interaction 4

Probenecid—Concurrent administration of lorazepam with probenecid decreases the total clearance of lorazepam.

Special Considerations

1. Contraindicated in patients with known hypersensitivity to benzodiazapines or any ingredients in the formulation.
2. Contraindicated in patients with acute angle-closure glaucoma.
3. Use with caution in geriatric patients, debilitated patients, and patients with underlying pulmonary disease.
4. Use with caution in patients with liver impairment.
5. Patients should be warned about the possibility of impaired ability to perform activities that require mental alertness or physical coordination, including operating machinery and driving.
6. Pregnancy category D.

Toxicity 1

Sedation, depression, headache, sleep disturbance, dizziness, weakness, and unsteadiness are most commonly observed.

Toxicity 2

Changes in appetite, nausea, and GI symptoms may occur infrequently.

Toxicity 3

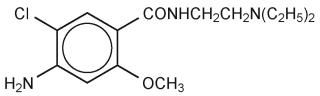
Reduction in blood pressure without clinical significance.

Toxicity 4

Transient amnesia or memory impairment.

M

Metoclopramide



Trade Name

Reglan

Classification

Substituted benzamide

Category

Antiemetic agent

Drug Manufacturer

Baxter and Geneva

Mechanism of Action

- Precise mechanism of antiemetic action is unclear.
- Acts centrally by directly blocking the dopamine receptors in the chemoreceptor trigger zone of the area postrema of brain.
- Acts peripherally to enhance the action of acetylcholine at muscarinic synapses.
- Stimulates GI motility through increasing gastric emptying via cholinergic excitatory processes.
- Inhibits 5-HT_3 receptors at high doses.

Absorption

Rapidly and completely absorbed by the GI tract. Peak plasma levels occur 1–2 hours after an oral dose.

Distribution

Extensively distributed to body tissues and crosses the blood-brain barrier. Distributes into the placenta and found in breast milk. Approximately 30% of drug is bound by plasma proteins.

Metabolism

Precise metabolism of drug has not been clearly established. Main routes of metabolism involve conjugation with glucuronic acid and sulfuric acid. Primary route of elimination is through the kidneys. About 85% of an administered dose is recovered as the parent compound and metabolites in the urine. Only 5% is eliminated via biliary excretion. The mean elimination half-life in adult cancer patients is approximately 5–6 hours.

Indications

1. Prevention and/or treatment of nausea and vomiting associated with cancer chemotherapy.
2. Prevention of postoperative nausea and vomiting.
3. Treatment of GI motility disorders, diabetic gastroparesis, and/or gastroesophageal reflux.

Dosage Range

1. Oral: Recommended dose is 20–40 mg PO every 4–6 hours as needed.
2. IV: Recommended dose is 2–3 mg/kg IV administered 30 minutes before chemotherapy and repeated 2 hours after chemotherapy up to 2 additional doses.

Drug Preparation

- Available as 5 and 10 mg tablets for oral use.
- Available as a 5 mg/mL or 10 mg/mL solution for oral use.
- Available as a 5 mg/mL solution in 2, 10, and 30 mL single-dose vials for IV use.
- Metoclopramide injection may be diluted in 50 mL 0.9% sodium chloride or 5% dextrose and infused over 15 minutes.
- Diluted solution is stable for 24 hours at room temperature.

Drug Interaction 1

CNS depressants—Metoclopramide may enhance the CNS effects of alcohol, analgesics, anesthetics, barbiturates, opiates, and sedatives.

Drug Interaction 2

Digoxin—Metoclopramide may decrease the oral absorption of digoxin.

Drug Interaction 3

Anticholinergic agents—The effects of metoclopramide on GI motility are antagonized by anticholinergic agents.

Drug Interaction 4

MAO inhibitors—Metoclopramide causes the release of catecholamines in patients with essential hypertension and should be used cautiously in patients receiving MAO inhibitors.

Special Considerations

1. Contraindicated in patients with pheochromocytoma as it may induce a hypertensive crisis.
2. Contraindicated in patients with seizure disorders because the frequency and severity of seizures may be increased.

3. Use with caution in patients with renal impairment. Dose adjustment is required in patients with decreased renal function.
4. Use with caution in patients with Parkinson's disease as parkinsonian symptoms may be worsened with metoclopramide.
5. Extrapyramidal symptoms typically occur within 24–48 hours of metoclopramide treatment. Most commonly seen with high-dose therapy and in pediatric patients and young adults. Diphenhydramine 50 mg IV or IM can provide immediate relief.
6. Use with caution in patients with a history of mental depression and/or suicidal tendencies as exacerbation or worsening of underlying depression may occur.
7. Pregnancy category B. Breast-feeding should be avoided.

Toxicity 1

Headache, fatigue, drowsiness, restlessness, and insomnia are the most common side effects (10%–15%).

Toxicity 2

Diarrhea and/or abdominal pain.

Toxicity 3

Dry mouth.

Toxicity 4

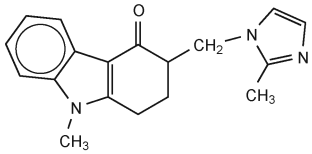
Hypersensitivity reactions with dyspnea, skin rash, urticaria, bronchospasm, and hypotension.

Toxicity 5

Extrapyramidal reactions with motor restlessness, tremor, akisthesia, dystonia, and tardive dyskinesia.

Ondansetron

O



Trade Name

Zofran

Classification

5-HT_3 receptor antagonist

Category

Antiemetic agent

Drug Manufacturer

GlaxoSmithKline

Mechanism of Action

- Competitive, highly selective antagonist of type 3, 5-HT_3 receptors.
- 5-HT_3 receptors are present centrally, in the chemoreceptor trigger zone of the area postrema of brain, and peripherally, on vagal nerve terminals. Antiemetic action of ondansetron may be mediated centrally, peripherally, or at both sites.
- Does not have direct dopamine-receptor antagonist activity.
- Effective in acute nausea and vomiting but plays only a limited role in delayed emesis.

Absorption

Well absorbed by the GI tract. Mean bioavailability in healthy subjects ranges from 48% to 75%.

Distribution

Nearly 40% of circulating drug is distributed in red blood cells.

Metabolism

Undergoes extensive metabolism in the liver by the cytochrome P450 microsomal system. The main metabolic pathway is hydroxylation followed by glucuronide or sulfate conjugation. Less than 5% of an administered dose is recovered as the parent compound in the urine. The mean elimination half-life in adult cancer patients is 4 hours.

Indications

1. Treatment of nausea and vomiting associated with moderately or highly emetogenic cancer chemotherapy.
2. Prevention and/or management of postoperative nausea and vomiting.
3. Prevention of nausea and vomiting associated with radiotherapy in patients receiving total body irradiation or single high-dose fraction or daily fractions to the abdomen.

Dosage Range

1. Oral: Recommended dose is 8 mg PO bid with the first dose given 30 minutes before chemotherapy. Continue for 1–2 days after chemotherapy is completed.
2. For the prevention of radiotherapy-induced nausea and vomiting, 8 mg PO to be taken 1–2 hours before radiotherapy and then 8 mg PO every 8 hours post radiotherapy.
3. IV: Recommended dose is a single 32 mg IV dose administered 30 minutes before chemotherapy or 0.15 mg/kg IV every 4 hours for 3 doses given 30 minutes before chemotherapy.

Drug Preparation

- Available as a 4 mg/5 mL clear to light yellow solution for oral use.
- Available as 4 and 8 mg disintegrating tablets for oral use.
- Available as 2 mg/mL single-dose or multidose vials or as 32 mg/50 mL premixed single-dose plastic containers.
- Mix solution in 5% dextrose or 0.9% sodium chloride and infuse over 15 minutes.

Drug Interaction 1

Inducers of hepatic cytochrome P450 enzymes—Inducers of the liver P450 system including alcohol, barbiturates, carbamazepine, efavirenz, griseofulvin, modafinil, nevirapine, phenylbutazone, phenytoin, rifabutin, rifampin, and rifapentine may change the clearance and the half-life of ondansetron. While no dosage adjustment is officially recommended, caution is warranted when any of these drugs are taken concurrently with ondansetron.

Drug Interaction 2

Inhibitors of hepatic cytochrome P450 enzymes—Inhibitors of the liver P450 system including allopurinol, amiodarone, amprenavir, MAO inhibitors, isoniazid, phenylbutazone, omeprazole, valproic acid, and verapamil may change the clearance and half-life of ondansetron. While no dosage adjustment is officially recommended, caution is recommended when any of these drugs are taken concurrently with ondansetron.

Special Considerations

1. Use with caution in patients with severe hepatic impairment as the clearance of ondansetron is decreased, resulting in an increased plasma half-life. Dose modification is warranted in such patients, and the total daily dose should not exceed 8 mg.
2. Ondansetron may, on rare occasions, cause hypersensitivity reactions. Patients should be warned of this possibility and be advised to contact their physician at the first sign of a skin rash or any other sign of hypersensitivity.
3. Use with caution in elderly patients, especially patients older than 75 years of age, as the plasma clearance may be decreased, resulting in increased drug levels.
4. Patients with phenylketonuria should be informed that oral tablets of ondansetron contain aspartame, which is metabolized in the GI tract to phenylalanine.
5. Pregnancy category B. Breast-feeding should be avoided.

Toxicity 1

Fever, headache, malaise, and fatigue occur in 10% of patients.

Toxicity 2

Constipation, diarrhea, and/or abdominal pain.

Toxicity 3

Transient elevations in LFTs. Usually clinically asymptomatic.

Toxicity 4

Local reaction at site of injection with pain, redness, and burning.

Toxicity 5

Hypersensitivity reactions with dyspnea, skin rash, urticaria, bronchospasm, and hypotension have been reported in rare instances.

P

Palonosetron

Trade Name

Aloxi

Classification

5-HT_3 receptor antagonist

Category

Antiemetic agent

Drug Manufacturer

MGI Pharma

Mechanism of Action

- Competitive, highly selective antagonist of type 3, 5-HT_3 receptors.
- 5-HT_3 receptors are present centrally, in the chemoreceptor trigger zone of the area postrema of brain, and peripherally, on vagal nerve terminals. Antiemetic action of palonosetron may be mediated centrally, peripherally, or at both sites.
- Does not have direct dopamine-receptor antagonist activity.
- Effective in both acute and delayed nausea and vomiting.

Absorption

Not available for oral use and is administered only via the parenteral route.

Distribution

Nearly 60% of circulating drug is bound to plasma proteins.

Metabolism

Undergoes metabolism by multiple routes with about 50% of parent drug metabolized to two main metabolites, N-oxide-palonosetron and 6-S-hydroxy-palonosetron. Each of these metabolites has less than 1% of the 5-HT_3 receptor antagonist activity of the parent compound. In vitro studies show that CYP2D6, CYP3A, and CYP12, to a much lesser extent, are involved in palonosetron metabolism. The mean elimination half-life in adult cancer patients is 40 hours.

Indications

1. Prevention of acute nausea and vomiting associated with initial and repeat courses of moderately or highly emetogenic cancer chemotherapy.
2. Prevention of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

Dosage Range

IV: Recommended dose is a single 0.25 mg IV dose administered 30 minutes before chemotherapy. Repeat dosing of drug within a seven day interval is not recommended as the safety and efficacy of consecutive and/or alternate dosing in patients has not been evaluated.

Drug Preparation

Available as 0.25 mg/5 mL single-use glass vials.

Drug Interactions

Potential for clinical significant drug interactions with palonosetron appears to be low.

Special Considerations

1. Use with caution in patients who have or may develop prolongation of cardiac conduction intervals, especially QTc. These include patients with hypokalemia or hypomagnesemia, patients taking diuretics with potential for inducing electrolyte abnormalities, patients with QT syndrome, patients taking anti-arrhythmic drugs or other drugs which lead to QT prolongation, and cumulative high dose anthracycline therapy.
2. Palonosetron may cause hypersensitivity reactions as has been observed with other 5-HT_3 receptor antagonists. Patients should be warned of this possibility and be advised to contact their physician at the first sign of a skin rash or any other sign of hypersensitivity.
3. Dose reduction is not required in patients with impaired liver and/or renal dysfunction.
4. Pregnancy category B. Breast-feeding should be avoided.

Toxicity 1

Headache occurs in 10% of patients.

Toxicity 2

Constipation, diarrhea, and/or abdominal pain.

Toxicity 3

Transient elevations in LFTs. Usually clinically asymptomatic.

Toxicity 4

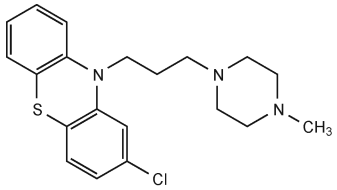
Somnolence, dizziness, insomnia, and fatigue. Anxiety and euphoric mood have also been observed.

Toxicity 5

Hypersensitivity reactions have been reported in rare instances.

P

Prochlorperazine



Trade Name

Compazine

Classification

Phenothiazine

Category

Antiemetic agent

Drug Manufacturer

GlaxoSmithKline

Mechanism of Action

- Precise mechanism of antiemetic action is unclear.
- Blocks dopamine receptors in the chemoreceptor trigger zone.
- Inhibits vagal stimulation of the vomiting center by peripheral afferents.

Absorption

Following oral administration of tablet form, onset of action is 30–40 minutes with 3–4 hours duration of action. Oral extended-release formulation prolongs duration of action up to 10–12 hours. Rectal suppository form has a 60-minute onset of action with 3–4 hours of duration. IM route has a 10–20 minutes onset of action and lasts for up to 12 hours.

Distribution

Large volume of distribution. Drug crosses the placenta and is excreted in breast milk.

Metabolism

Metabolism occurs in the liver with excretion mainly in the kidneys. Terminal elimination half-life is 7–8 hours.

Indications

1. Control of nausea and vomiting of various etiologies.
2. Management of the manifestations of psychotic disorders.

3. Acute treatment of generalized nonpsychotic anxiety.

Dosage Range

1. Oral: Recommended dose is 5–25 mg PO every 6 hours. For the slow-release form, dose ranges from 10 to 30 mg PO every 12 hours.
2. Rectal: Recommended dose is 25 mg per rectum (PR) every 12 hours.
3. IM: Recommended dose is 5–25 mg IM every 6 hours.
4. IV: Recommended dose is 5–25 mg IV every 6 hours.

Drug Preparation

- Available as 5 and 10 mg tablets, 10 and 15 mg extended-release capsules, and 5 mg/mL syrup for oral use.
- Available as 2.5, 5, and 25 mg suppositories for rectal use.
- Available in 5 mg/mL vials for IV use.
- Store in tight, light-resistant containers.

Drug Interaction 1

Oral anticoagulants—Patients receiving coumarin-derived anticoagulants should be closely monitored for alterations in their clotting parameters (PT and INR) as prochlorperazine may diminish their clinical efficacy.

Drug Interaction 2

Thiazide diuretics—Concurrent use of prochlorperazine with thiazide diuretics may accentuate orthostatic hypotension.

Drug Interaction 3

Propranolol—Prochlorperazine may cause elevation of plasma levels of propranolol.

Drug Interaction 4

Phenytoin—Prochlorperazine may interfere with the hepatic metabolism of phenytoin and thereby enhance phenytoin-associated drug toxicity.

Special Considerations

1. Contraindicated in patients with known hypersensitivity to phenothiazines.
2. Use with caution in patients who are receiving CNS depressants.
3. Use with caution in elderly patients.
4. Use with caution in patients with glaucoma.
5. Patients should be advised to avoid heat exposure as prochlorperazine may interfere with thermoregulatory mechanisms.

6. Use with caution in patients under the age of 35 years as there is an increased risk of dystonic reactions.
7. Patients should be advised to avoid sun exposure to prevent photosensitivity reactions.

Toxicity 1

Drowsiness, sedation, insomnia, dizziness, and blurred vision.

Toxicity 2

Extrapyramidal reactions in the form of motor restlessness, tremor, akathisia, dystonia, pseudoparkinsonism, and tardive dyskinesia.

Toxicity 3

Dry mouth, constipation.

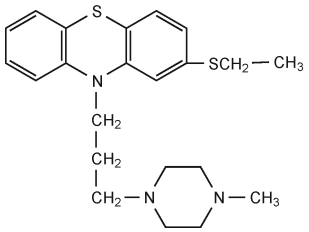
Toxicity 4

Orthostatic hypotension.

Toxicity 5

Mild photosensitivity, skin rash, and urticaria.

Thiethylperazine



Trade Name

Torecan

Classification

Phenothiazine

Category

Antiemetic agent

Drug Manufacturer

Roxane

Mechanism of Action

- Precise mechanism of antiemetic action is unclear.
- Blocks dopamine receptors in the chemoreceptor trigger zone.
- Inhibits vagal stimulation of the vomiting center by peripheral afferents.

Absorption

Following oral administration of tablet form, onset of action is 30–40 minutes with 3–4 hours duration of action. Rectal suppository form has a 45–60 minute onset of action with up to 4 hours duration.

Distribution

Large volume of distribution. Drug crosses the placenta and is excreted in breast milk.

Metabolism

Metabolism occurs in the liver with excretion mainly in the kidneys. Terminal elimination half-life is 7–8 hours.

Indications

Prevention and/or treatment of nausea and vomiting of various etiologies.

Dosage Range

1. Oral: Recommended dose is 10 mg PO 1–3 times daily.
2. Rectal: Recommended dose is 10 mg PR 1–3 times daily.
3. IM: Recommended dose is 10 mg IM 1–3 times daily.

Drug Preparation

- Available as 10 mg tablets for oral use.
- Available as 2.5, 5, and 25 mg suppositories for rectal use.
- Available in 5 mg/mL ampules for IM use.

Drug Interaction 1

Barbiturates—Antiemetic effect of thiethylperazine may be decreased in the presence of barbiturates, and dose may need to be increased.

Drug Interaction 2

Antacids—Concurrent use of antacids with thiethylperazine may decrease its absorption. For this reason, thiethylperazine should be administered 2 hours before or after antacid therapy.

Special Considerations

1. Contraindicated in patients with known hypersensitivity to phenothiazines.
2. Contraindicated in patients with severe CNS depression or in a comatose state.
3. Contraindicated in patients with a known allergy to tartrazine dye as it may induce allergic reactions including bronchial asthma.
4. Contraindicated in patients with sulfite allergy as the IV formulation contains sodium metabisulfite.
5. Contraindicated in women who are pregnant. Breast-feeding should be avoided.
6. Use with caution in patients under the age of 35 years as there is an increased risk of dystonic reactions.
7. Patients should be advised to avoid driving or operating machinery after taking thiethylperazine.
8. Patients should be cautioned about combined CNS effects when thiethylperazine is taken with alcohol or other CNS depressants.

Toxicity 1

Drowsiness, sedation, insomnia, dizziness, and headache.

Toxicity 2

Extrapyramidal reactions in the form of motor restlessness, tremor, akathisia, dystonia, pseudoparkinsonism, and tardive dyskinesia. Seizures have been reported.

Toxicity 3

Dry mouth and nose, blurred vision, constipation, and paralytic ileus.

Toxicity 4

Orthostatic hypotension.

COMMON ANTIEMETIC REGIMENS CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

Mildly Emetogenic Chemotherapy (Levels 1 and 2):

1. Prochlorperazine 5–25 mg PO, 5–25 IV, or 25 mg PR before chemotherapy and then 5–25 mg PO every 6 hours as needed.
2. Thiethylperazine 10 mg PO, 10 mg IM, or 10 mg PR.
3. Ondansetron 8 mg PO bid with the first dose 30 minutes before the start of chemotherapy and a subsequent dose 8 hours after the first dose or 32 mg IV.
4. Dexamethasone 4–8 mg PO or 10–20 mg IV.
5. Prochlorperazine 5–25 mg PO, 5–25 mg IV, or 25 mg PR before chemotherapy and then 5–25 mg PO every 6 hours as needed; dexamethasone 4 mg PO or 10–20 mg IV before chemotherapy and continue with 4 mg PO every 6 hours up to a total of 4 doses as needed.
6. Prochlorperazine 5–25 mg PO, 5–25 mg IV, or 25 mg PR before chemotherapy and then 5–25 mg PO every 6 hours as needed; dexamethasone 4 mg PO or 10–20 mg IV before chemotherapy and continue with 4 mg PO every 6 hours up to a total of 4 doses as needed; and lorazepam 1.5 mg/m^2 IV administered 45 minutes before chemotherapy.

Moderately Emetogenic Chemotherapy (Level 3):

1. Ondansetron 32 mg IV and dexamethasone 4–8 mg PO or 10–20 mg IV given 30 minutes before chemotherapy. In the next 1–2 mornings, give ondansetron 16 mg PO and dexamethasone 8 mg PO along with prochlorperazine 10 mg PO every 6 hours as needed.
2. Dolasetron 100 mg PO or IV and dexamethasone 8 mg IV 30 minutes before chemotherapy. In the next 1–2 mornings, give dolasetron 100 mg PO and dexamethasone 8 mg PO along with prochlorperazine 10 mg PO every 6 hours as needed.
3. Granisetron 1–2 mg PO 1 hour before chemotherapy or 1 mg or 10 μg/kg IV and dexamethasone 8 mg IV 30 minutes before chemotherapy. In the next 1–2 mornings, give granisetron 1 mg PO and dexamethasone 8 mg PO along with prochlorperazine 10 mg PO every 6 hours as needed.
4. Aprepitant 125 mg PO taken 60 minutes before chemotherapy; dexamethasone 12 mg PO and odansetron 32 mg IV given 30 minutes before chemotherapy.

5. Aprepitant 125 mg PO taken 60 minutes before chemotherapy; dexamethasone 12 mg PO and granisetron 1–2 mg PO or 10 μg/kg IV given 30 minutes before chemotherapy.
6. Dexamethasone 4–8 mg PO or 10–20 mg IV for 1 dose before chemotherapy; lorazepam 1.5 mg/m² IV before chemotherapy; and prochlorperazine 5–25 mg PO or IV before chemotherapy.
7. Palonosetron 0.25 mg IV given 30 minutes before chemotherapy.

Highly Emetogenic Chemotherapy (Levels 4 and 5):

1. Ondansetron 32 mg IV and dexamethasone 10–20 mg IV plus lorazepam 1 mg PO or IV given 30 minutes before chemotherapy and then every 6 hours as needed. Ondansetron 16 mg PO and dexamethasone 8 mg PO in the next 2–3 mornings along with prochlorperazine 10 mg PO every 6 hours as needed.
2. Dolasetron 100 mg IV and dexamethasone 10–20 mg IV 30 minutes before chemotherapy or the same doses given orally 1 hour before chemotherapy. Dolasetron 100 mg PO and dexamethasone 8 mg PO in the next 2–3 mornings along with prochlorperazine 10 mg PO every 6 hours as needed.
3. Dolasetron 200 mg PO and dexamethasone 20 mg PO 30 minutes before chemotherapy.
4. Granisetron 1–2 mg or 10 μg/kg IV and dexamethasone 10–20 mg IV 30 minutes before chemotherapy. Granisetron 1 mg PO and dexamethasone 8 mg PO in the next 2–3 mornings along with prochlorperazine 10 mg PO every 6 hours as needed.
5. Aprepitant 125 mg PO taken 60 minutes before chemotherapy; dexamethasone 12 mg PO and odansetron 32 mg IV given 30 minutes before chemotherapy.
6. Aprepitant 125 mg PO taken 60 minutes before chemotherapy; dexamethasone 12 mg PO and granisetron 1–2 mg PO or 10 μg/kg IV given 30 minutes before chemotherapy.
7. Metoclopramide 2–3 mg/kg IV, dexamethasone 10–20 mg IV; and diphenhydramine 25–50 mg IV to be given 1 hour before chemotherapy or orally at the dame doses 30 minutes before chemotherapy. Metoclopramide 20–40 mg PO, dexmethasone 8 mg PO in the next 2–3 mornings along with prochlorperazine 10 mg PO every 6 hours as needed.
8. Metoclopramide 2–3 mg/kg IV before chemotherapy and then 2 hours post chemotherapy; dexamethasone 10–20 mg IV; diphenhydramine 25–50 mg IV; and lorazepam 1–2 mg IV.
9. Palonosetron 0.25 mg IV given 30 minutes before chemotherapy.

COMMON REGIMENS FOR DELAYED AND/OR BREAKTHROUGH NAUSEA AND VOMITING:

1. Metoclopramide 40 mg PO every 4–6 hours and dexamethasone 4–8 mg PO every 4–6 hours for 4 days.
2. Metoclopramide 40 mg PO every 4–6 hours; dexamethasone 4–8 mg PO every 4–6 hours; and prochlorperazine 10–25 mg PO every 6 hours.
3. Aprepitant 80 mg PO and dexamethasone 8 mg PO once daily on days 2 and 3.
4. Ondansetron 8 mg PO bid for up to 2–3 days after chemotherapy.
5. Ondansetron (orally dissolving tablets) 8 mg sublingual every 8 hours as needed.
6. Metoclopramide 20–40 mg PO and diphenhydramine 50 mg PO every 3–4 hours.
7. Prochlorperazine suppository 25 mg PR every 12 hours.

Table 1. Emetogenic Potential of Chemotherapy Agents

Level	*Frequency of Emesis (%)*	*Agent*
5	> 90	Actinomycin-D
		Carmustine ≤ 250 mg/m²
		Cisplatin > 50 mg/m²
		Cyclophosphamide > 1,500 mg/m²
		Dacarbazine > 500 mg/m²
		Mechlorethamine
		Pentostatin
		Streptozocin
4	60–90	Carboplatin
		Carmustine ≤ 250 mg/m²
		Cisplatin < 50 mg/m²
		Cyclophosphamide 750–1,500 mg/m²
		Cytarabine > 1 g/m²
		Doxorubicin > 60 mg/m²
		Irinotecan

Table 1 (cont.)

Level	*Frequency of Emesis (%)*	*Agent*
		Melphalan (IV)
		Methotrexate > 1,000 mg/m^2
		Procarbazine
3	30–60	Aldesleukin
		Altretamine
		Cyclophosphamide ≤ 750 mg/m^2
		Cyclophosphamide (oral)
		Cytarabine (conventional doses)
		Doxorubicin 20–60 mg/m^2
		Epirubicin ≤ 90 mg/m^2
		5-Fluorouracil (high doses)
		Idarubicin
		Ifosfamide
		Methotrexate 250–1,000 mg/m^2
		Mitoxantrone < 15 mg/m^2
2	10–30	Asparaginase
		Cytarabine < 1 g/m^2
		Daunorubicin
		Docetaxel
		Doxorubicin < 20 mg/m^2
		Etoposide
		5-Fluorouracil < 1,000 mg/m^2
		Gemcitabine
		Lomustine
		Methotrexate 50–250 mg/m^2
		Mitomycin-C
		Paclitaxel
		Teniposide
		Thiotepa
		Topotecan
1	< 10	Bleomycin

Table 1 (cont.)

Level	*Frequency of Emesis (%)*	*Agent*
		Busulfan
		Chlorambucil (oral)
		Cladribine
		Fludarabine
		Hydroxyurea
		Interferon
		Melphalan (oral)
		Mercaptopurine
		Methotrexate ≤ 50 mg/m^2
		L-Phenylalanine mustard (oral)
		Thioguanine (oral)
		Tretinoin
		Vinblastine
		Vincristine
		Vinorelbine

Adapted and taken from: Hesketh et al. *J Clin Oncol* 1997; 15: 103–9 and Gralla et al. *J Clin Oncol* 1998; 17: 2971–2994.

Single agents are divided into five different levels of emetogenic potential. They are as follows:

1. Level 1: < 10% of patients experience acute (< 24 hours after chemotherapy) emesis without antiemetic prophylaxis.
2. Level 2: 10%–30% of patients experience acute emesis without antiemetic prophylaxis.
3. Level 3: 30%–60% of patients experience acute emesis without antiemetic prophylaxis.
4. Level 4: 60%–90% of patients experience acute emesis without antiemetic prophylaxis.
5. Level 5: > 90% of patients experience acute emesis without antiemetic prophylaxis.

With regard to combination regimens, the emetogenic levels are determined by identifying the most emetogenic agent in the combination and then assessing the relative contribution of the other agents based on the following:

1. Level 1 agents do not contribute to the emetogenic potential of the combination.
2. The presence of one or more level 2 agents increases the emetogenic potential of the combination by one level greater than the most emetogenic agent in the combination.
3. The presence of level 3 or level 4 agents increases the emetogenic potential of the combination by one level per given agent.

3
Guidelines for Chemotherapy and Dosing Modifications

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Dawn Tiedemann, and Edward Chu

Successful administration of chemotherapy relies on several critical factors, including the patient's age; performance status; co-morbid illnesses; and baseline hematologic, hepatic, and renal status. The dose of a given chemotherapeutic agent must be adjusted accordingly to reflect these parameters, as well as any specific drug-induced toxicities that may have been experienced with prior treatment. This chapter outlines performance scales that have been established to determine a patient's functional status; reviews methods to determine creatinine clearance, body surface area, and drug dose; and provides recommendations for dosing in the setting of myelosuppression, hepatic dysfunction, and renal dysfunction. General guidelines for dialyzing chemotherapeutic agents in the setting of drug overdose or renal failure are provided, and the extravasation potential of various agents is reviewed. A more detailed review for each individual drug is provided in Chapter 2, and the reader is advised to refer to the published literature for further details regarding specific guidelines for drug precautions and dose modifications.

Table 1. Performance Scales

Karnofsky

(%)	*Performance*
100	Normal, no evidence of disease
90	Able to carry on normal activity, minor signs or symptoms of disease
80	Normal activity with effort, some signs or symptoms of disease
70	Unable to perform normal activity, cares for self
60	Requires occasional assistance
50	Requires considerable assistance and frequent medical care
40	Disabled, requires special care and assistance
30	Severely disabled, hospitalization may be required
20	Hospitalization necessary for support, very sick
10	Moribund, rapid progression of disease
0	Dead

ECOG

(%)	*Performance*
0	Asymptomatic, normal activity
1	Fully ambulatory, symptomatic, able to perform activities of daily living
2	Symptomatic, up and about, in bed less than 50% of time
3	Symptomatic, capable of only limited self-care, in bed more than 50% of time
4	Completely disabled, cannot perform any self-care, bedridden 100% of time
5	Dead

Table 2. Determination of Creatinine Clearance

- The creatinine clearance is determined by the Cockcroft-Gault formula (Cockcroft, DW, Gault, MH. *Nephron* 1976; 16: 31–34), which takes into account age, weight, and serum creatinine.

$$\text{Males: Creatinine Clearance (mL/min)} = \frac{\text{weight (kg)} \times (140\text{-age})}{72 \times \text{serum creatinine (mg/dL)}}$$

$$\text{Females: Creatinine Clearance (mL/min)} = \frac{\text{weight (kg)} \times (140\text{-age}) \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

- The creatinine clearance can also be determined from a timed urine collection.

$$\text{Creatinine Clearance} = \frac{\text{urine creatinine}}{\text{serum creatinine}} \times \frac{\text{urine volume}}{\text{time}}$$

Table 3. Determination of Target Area Under the Curve (AUC)

The area under AUC refers to the area under the drug concentration × time curve, and it provides a measure of total drug exposure. It is expressed in concentration × units (mg/mL × min).

A formula for quantifying exposure to carboplatin based on dose and renal function was developed by Calvert et al. (Calvert, H, et al. *J Clin Oncol* 1989;7:1748–1756) and is as follows:

Carboplatin Dose (mg) = target AUC (mg/mL × min) × [GFR (mL/min) + 25]

It is important to note that the total dose is in mg and **NOT** mg/m^2. Target AUC is usually between 5 and 7 mg/mL/min for previously untreated patients. In previously treated patients, lower AUCs (between 4 and 6 mg/mL/min) are recommended. AUCs > 7 are generally not associated with improved response rates.

Table 4. Determination of Drug Dose

- Drug doses are calculated according to body surface area (BSA, mg/m^2).
- BSA is typically determined by using a nomogram scale or by using a BSA calculator.
- Once the BSA is determined, multiply the BSA by the amount of drug specified in the regimen to give the total dose of drug to be administered.

- For obese patients, ideal body weight (IBW), as opposed to the actual body weight, may be used to calculate BSA. It is important to refer to an IBW table to determine the IBW based on the individual's actual height. Once the IBW is determined, add one-third of the IBW to the IBW, which is then used to determine the BSA.
- IBW can be calculated from the following formulas:
  IBW for men (kg): 50.0 kg + 2.3 kg per inch over 5 feet
  IBW for women (kg): 45.5 kg + 2.3 kg per inch over 5 feet

Taken from: Olin B (Ed): "Drug Facts and Comparisons" St. Louis, Missouri, 1996.

Table 5. Calculation of Body Surface Area in Adult Amputees

Body Part	*% Surface Area of Amputated Part*
Hand and 5 fingers	3.0
Lower part of arm	4.0
Upper part of arm	6.0
Foot	3.0
Lower part of leg	6.0
Thigh	12.0

BSA (m^2) = BSA - [(BSA) × ($\%BSA_{part}$)], where BSA = body surface area, BSA_{part} = body surface area of amputated part.

Taken from: Colangelo, PM, et al. *Am J Hosp Pharm* 1984;41:2650–2655.

Table 6. General Guidelines for Percentage of Chemotherapy Dosage Based on Hematologic Parameters

	Granulocytes (× 10^6 cells)			
Platelets	*> 2.0*	*1.5–1.99*	*1–1.49*	*< 1.0*
> 100,000	100.0	75.0	50.0	0.0
50,000–99,000	50.0	50.0	50.0	0.0
< 50,000	0.0	0.0	0.0	0.0

Table 7. General Guidelines for Chemotherapy Dosage Based on Hepatic Function

Drug	*Recommended Dose Reduction for Hepatic Dysfunction*
Alemtuzumab	N/A
Altretamine	No dose reduction is necessary.
Amifostine	No dose reduction is necessary.
Aminoglutethimide	No dose reduction is necessary.
Amsacrine	Reduce dose by 25% if bilirubin > 2.0 mg/dL.
Anastrozole	No formal recommendation for dose reduction. Dose reduction may be necessary in patients with hepatic dysfunction.
Arsenic trioxide	No dose reduction is necessary.
L-Asparaginase	No dose reduction is necessary.
Bicalutamide	No formal recommendation for dose reduction. Dose reduction may be necessary if bilirubin > 3.0 mg/dL.
Bleomycin	No dose reduction is necessary.
Buserelin	No dose reduction is necessary.
Busulfan	No dose reduction is necessary.
Capecitabine	No dose reduction is necessary.
Carboplatin	No dose reduction is necessary.
Carmustine	No dose reduction is necessary.
Chlorambucil	No dose reduction is necessary.
Cisplatin	No dose reduction is necessary.
Cladribine	No dose reduction is necessary.
Cyclophosphamide	Reduce by 25% if bilirubin 3.0–5.0 mg/dL or SGOT > 180 mg/dL. Omit if bilirubin > 5.0 mg/dL.
Cytarabine	No formal recommendation for dose reduction. Dose reduction may be necessary in patients with hepatic dysfunction.
Dacarbazine	No dose reduction is necessary.
Dactinomycin	Reduce dose by 50% if bilirubin > 3.0 mg/dL.
Daunorubicin	Reduce dose by 25% if bilirubin 1.5–3.0 mg/dL. Reduce dose by 50% if bilirubin > 3.0 mg/dL. Omit if bilirubin > 5.0 mg/dL.

Table 7. (cont)

Drug	*Recommended Dose Reduction for Hepatic Dysfunction*
Docetaxel	Omit if bilirubin > 1.5 mg/dL, SGOT > 60 mg/dL, or alkaline phosphatase > 2.5 × upper limit of normal.
Doxorubicin	Reduce dose by 50% if bilirubin 1.5–3.0 mg/dL.
	Reduce dose by 75% if bilirubin 3.1–5.0 mg/dL.
	Omit if bilirubin > 5.0 mg/dL.
Doxorubicin liposome	Reduce dose by 50% if bilirubin 1.5–3.0 mg/dL.
	Reduce dose by 75% if bilirubin 3.1–5.0 mg/dL.
	Omit if bilirubin > 5.0 mg/dL.
Estramustine	No dose reduction is necessary.
Etoposide	Reduce dose by 50% if bilirubin 1.5–3.0 mg/dL or SGOT 60–180 mg/dL.
	Omit if bilirubin > 3 mg/dL or SGOT > 180 mg/dL.
Etoposide phosphate	Reduce dose by 50% if bilirubin 1.5–3.0 mg/dL or SGOT 60–180 mg/dL.
	Omit if bilirubin > 3 mg/dL or SGOT > 180 mg/dL.
Floxuridine	No dose reduction is necessary.
Fludarabine	No dose reduction is necessary.
5-Fluorouracil	Omit if bilirubin > 5.0 mg/dL.
Flutamide	No formal recommendation for dose reduction. Dose reduction may be necessary if bilirubin > 3.0 mg/dL.
Gemcitabine	No dose reduction is necessary.
Goserelin	No dose reduction is necessary.
Hydroxyurea	No dose reduction is necessary.
Idarubicin	Reduce dose by 25% if bilirubin 1.5–3.0 mg/dL or SGOT 60–180 mg/dL.
	Reduce dose by 50% if bilirubin 3.0–5.0 or SGOT > 180 mg/dL.
	Omit if bilirubin > 5.0 mg/dL.
Ifosfamide	No dose reduction is necessary.

Table 7. (cont)

Drug	*Recommended Dose Reduction for Hepatic Dysfunction*
Imatinib	Omit if bilirubin > 3 mg/dL or SGOT > 5 × ULN. Once bilirubin < 1.5 or SGOT < 2.5 × ULN, reduce dose from 400 mg to 300 mg or from 600 mg to 400 mg.
Interferon-alpha	No dose reduction is necessary.
Interleukin-2	Omit if signs of hepatic failure (ascites, encephalopathy, jaundice) are observed. Do NOT restart sooner than 7 weeks after recovery from severe hepatic dysfunction.
Irinotecan	No formal recommendation for dose reduction in the presence of hepatic dysfunction. Dose reduction may be necessary.
Isotretinoin	No formal recommendation for dose reduction in the presence of hepatic dysfunction. Dose reduction may be necessary.
Leucovorin	No dose reduction is necessary.
Leuprolide	No dose reduction is necessary.
Lomustine	No dose reduction is necessary.
Mechlorethamine	No dose reduction is necessary.
Megestrol acetate	No dose reduction is necessary.
Melphalan	No dose reduction is necessary.
6-Mercaptopurine	No dose reduction is necessary.
Mesna	No dose reduction is necessary.
Methotrexate	Reduce dose by 25% if bilirubin 3.1–5.0 mg/dL or SGOT > 180 mg/dL. Omit if bilirubin > 5.0 mg/dL.
Mitomycin-C	No dose reduction is necessary.
Mitotane	No formal recommendation for dose reduction in the presence of hepatic dysfunction. Dose reduction may be necessary.
Mitoxantrone	Reduce dose by 25% if bilirubin > 3.0 mg/dL.
Nilutamide	No formal recommendation for dose reduction. Dose reduction may be necessary if bilirubin > 3.0 mg/dL.
Oxaliplatin	N/A

Table 7. (cont)

Drug	*Recommended Dose Reduction for Hepatic Dysfunction*
Paclitaxel	No formal recommendation for dose reduction if bilirubin 1.5–3.0 mg/dL or SGOT 60–180 mg/dL. Omit if bilirubin > 5.0 mg/dL or SGOT > 180 mg/dL.
Pegasparaginase	No dose reduction is necessary.
Pemetrexed	No dose reduction is necessary.
Pentostatin	No dose reduction is necessary.
Procarbazine	No formal recommendation for dose reduction in the presence of hepatic dysfunction. Dose reduction may be necessary.
Rituximab	No dose reduction is necessary.
Streptozocin	No dose reduction is necessary.
Tamoxifen	No dose reduction is necessary.
Temozolomide	No dose reduction is necessary.
Thalidomide	N/A
Thioguanine	Omit if bilirubin > 5.0 mg/dL.
Thiotepa	No formal recommendation for dose reduction in the presence of hepatic dysfunction. Dose reduction may be necessary.
Topotecan	No dose reduction is necessary.
Trastuzumab	N/A
Tretinoin	Reduce dose to a maximum of 25 mg/m² if bilirubin 3.1–5.0 mg/dL or SGOT > 180 mg/dL. Omit if bilirubin > 5.0 mg/dL.
UFT	No dose reduction is necessary.
Vinblastine	No dose reduction if bilirubin < 1.5 mg/dL and SGOT < 60 mg/dL. Reduce by 50% if bilirubin 1.5–3.0 mg/dL and SGOT 60–180 mg/dL. Omit if bilirubin > 3.0 mg/dL or SGOT > 180 mg/dL.
Vincristine	No dose reduction if bilirubin < 1.5 mg/dL and SGOT < 60 mg/dL. Reduce by 50% if bilirubin 1.5–3.0 mg/dL and SGOT 60–180 mg/dL.

Table 7. (cont)

Drug	*Recommended Dose Reduction for Hepatic Dysfunction*
	Omit if bilirubin > 3.0 mg/dL or SGOT > 180 mg/dL.
Vinorelbine	No dose reduction if bilirubin < 2.0 mg/dL. Reduce dose by 50% if bilirubin 2.0–3.0 mg/dL. Reduce dose by 75% if bilirubin 3.1–5.0 mg/dL. Omit if bilirubin > 5.0 mg/dL.

N/A–not available

ULN–upper limit of normal

Table 8. General Guidelines for Chemotherapy Dosage Based on Renal Function

Drug	*Recommended Dose Reduction for Renal Dysfunction*
Alemtuzumab	N/A
Altretamine	N/A
Amifostine	N/A
Aminoglutethimide	N/A
Amsacrine	N/A
Anastrozole	No dose reduction is necessary.
Arsenic trioxide	No formal recommendation for dose reduction in the presence of renal dysfunction. Dose reduction may be necessary.
L-Asparaginase	Omit if CrCl < 60 mL/min.
Bicalutamide	No dose reduction is necessary.
Bleomycin	No dose reduction if CrCl > 60 mL/min. Reduce dose by 25% if CrCl 10–60 mL/min. Reduce dose by 50% if CrCl < 10 mL/min.
Buserelin	N/A
Busulfan	No dose reduction is necessary.
Capecitabine	Reduce dose by 25% if CrCl 30–50 mL/min. Omit if CrCl < 30 mL/min.
Carboplatin	No dose reduction if CrCl > 60 mL/min. AUC dose is modified according to CrCl.

Table 8. (cont)

Drug	*Recommended Dose Reduction for Renal Dysfunction*
Carmustine	Omit if CrCl < 60 mL/min.
Chlorambucil	No dose reduction is necessary.
Cisplatin	No dose reduction if CrCl > 60 mL/min. Reduce dose by 50% if CrCl 30–60 mL/min. Omit if CrCl < 30 mL/min.
Cladribine	N/A
Cyclophosphamide	No dose reduction if CrCl > 50 mL/min. Reduce dose by 25% if CrCl 10–50 mL/min. Reduce dose by 50% if CrCl < 10 mL/min.
Cytarabine	No formal recommendation for dose reduction in the presence of renal dysfunction. Dose reduction may be necessary.
Dacarbazine	No formal recommendation for dose reduction in the presence of renal dysfunction. Dose reduction may be necessary.
Dactinomycin	N/A
Daunorubicin	Reduce dose by 50% if serum creatinine > 3.0 mg/dL.
Dexrazoxane	N/A
Docetaxel	No dose reduction is necessary.
Doxorubicin	No dose reduction is necessary.
Doxorubicin liposome	No dose reduction is necessary.
Estramustine	N/A
Etoposide	No dose reduction if CrCl > 50 mL/min. Reduce dose by 25% if CrCl 10–50 mL/min. Reduce dose by 50% if CrCl < 10 mL/min.
Etoposide phosphate	No dose reduction if CrCl > 50 mL/min. Reduce dose by 25% if CrCl 10–50 mL/min. Reduce dose by 50% if CrCl < 10 mL/min.
Floxuridine	N/A
Fludarabine	No formal recommendation for dose reduction in the presence of renal dysfunction. Dose reduction may be necessary.
5-Fluorouracil	No dose reduction is necessary.
Flutamide	N/A

Table 8. (cont)

Drug	*Recommended Dose Reduction for Renal Dysfunction*
Gemcitabine	No dose reduction is necessary.
Goserelin	No dose reduction is necessary.
Hydroxyurea	Reduce dose by 80% if CrCl < 10 mL/min.
Idarubicin	No dose reduction is necessary.
Ifosfamide	N/A
Imatinib	No dose reduction is necessary.
Interferon-alpha	No dose reduction is necessary.
Interleukin-2	Omit or discontinue if serum creatinine > 4.5 mg/dL or serum creatinine > 4.0 mg/dL in the presence of fluid overload.
Irinotecan	No dose reduction is necessary.
Isotretinoin	N/A
Leucovorin	No dose reduction is necessary.
Leuprolide	N/A
Lomustine	Omit if CrCl < 60 mL/min.
Mechlorethamine	N/A
Megestrol acetate	N/A
Melphalan	No dose reduction is necessary. However, use with caution in the presence of renal dysfunction.
6-Mercaptopurine	No formal recommendation for dose reduction in the presence of renal dysfunction. Adjust for renal dysfunction by either increasing the interval or decreasing the dose.
Mesna	N/A
Methotrexate	No dose reduction is necessary if CrCl > 60 mL/min. Reduce by 50% if CrCl 30–60 mL/min. Omit if CrCl < 30 mL/min.
Mitomycin-C	No dose reduction is necessary if CrCl > 60 mL/min. Reduce dose by 25% if CrCl 10–60 mL/min. Reduce dose by 50% if CrCl < 10 mL/min.
Mitotane	N/A
Mitoxantrone	No dose reduction is necessary.
Nilutamide	No dose reduction is necessary.

Table 8. (cont)

Drug	*Recommended Dose Reduction for Renal Dysfunction*
Oxaliplatin	N/A
Paclitaxel	No dose reduction is necessary.
Pegasparaginase	N/A
Pemetrexed	Dose reduction is necessary when CrCl < 60 mL/min. and in proportion to the reduction in CrCl.
Pentostatin	No formal recommendation for dose reduction in the presence of renal dysfunction. Dose reduction may be necessary if CrCl 30–60 mL/min.
Procarbazine	Omit if CrCl < 30 mL/min.
Rituximab	N/A
Streptozocin	Omit if CrCl < 60 mL/min.
Tamoxifen	No dose reduction is necessary.
Temozolomide	N/A
Thalidomide	N/A
Thioguanine	N/A
Thiotepa	No formal recommendation for dose reduction in the presence of renal dysfunction. Dose reduction may be necessary.
Topotecan	No dose reduction is necessary if CrCl > 60 mL/min. Reduce dose by 50% if CrCl 10–60 mL/min. Omit if CrCl < 10 mL/min.
Trastuzumab	N/A
Tretinoin	Give a maximum of 25 mg/m² in the presence of renal dysfunction. No dose reduction is necessary.
UFT	No dose reduction is necessary.
Vinblastine	
Vincristine	No dose reduction is necessary.
Vinorelbine	No dose reduction is necessary.

CrCl–creatinine clearance

N/A–not available

Table 9. Guidelines for Dialysis of Chemotherapy Drugs

	Hemodialysis			Peritoneal Dialysis		
Drug	**YES**	**NO**	**UNKNOWN**	**YES**	**NO**	**UNKNOWN**
Alemtuzumab			X			X
Altretamine			X			X
Aminoglutethimide	X					X
Amsacrine			X			X
Anastrozole			X			X
Arsenic trioxide			X			X
Bicalutamide			X			X
Bleomycin		X				X
Buserelin			X			X
Busulfan			X			X
Capecitabine			X			X
Carboplatin	X				X	
Carmustine		X				X
Chlorambucil			X			X
Cisplatin	X					X
Cladribine			X			X
Cyclophosphamide	X					X
Cytarabine			X		X	
Dacarbazine			X			X
Dactinomycin			X			X
Daunorubicin			X			X
Docetaxel			X			X
Doxorubicin		X				X
Doxorubicin liposome			X			X
Estramustine			X			X
Etoposide		X				X
Etoposide phosphate			X			X
Floxuridine			X			X
Fludarabine			X			X
5-Fluorouracil			X			X
Flutamide			X			X
Gemcitabine			X			X
Goserelin			X			X
Hydroxyurea			X			X
Idarubicin			X			X

Table 9. (cont)

	Hemodialysis			Peritoneal Dialysis		
Drug	*YES*	*NO*	*UNKNOWN*	*YES*	*NO*	*UNKNOWN*
Ifosfamide			X			X
Imatinib			X			X
Irinotecan			X			X
Isotretinoin			X			X
Leuprolide			X			X
Lomustine		X				X
Mechlorethamine			X			X
Megestrol acetate			X			X
Melphalan			X			X
6-Mercaptopurine			X			X
Methotrexate	X				X	
Mitomycin-C			X			X
Mitotane			X			X
Mitoxantrone			X			X
Nilutamide			X			X
Oxaliplatin			X			X
Paclitaxel			X			X
Pentostatin			X			X
Procarbazine			X			X
Rituximab			X			X
Streptozocin			X			X
Tamoxifen			X			X
Temozolomide			X			X
Thalidomide			X			X
Thioguanine			X			X
Thiotepa			X			X
Topotecan			X			X
Trastuzumab			X			X
Vinblastine			X			X
Vincristine			X			X
Vinorelbine			X			X

Table 10. Local Skin Toxicity Associated with Administration of Chemotherapy Drugs

Drug	*VESICANT*	*IRRITANT*
Aldesleukin	No	No
Amifostine	No	No
Amsacrine	Yes	No
L-Asparaginase	No	No
Bacillus Calmette-Guérin	No	No
Bleomycin	No	Yes
Busulfan	No	No
Carboplatin	No	Yes
Carmustine	No	Yes
Cisplatin	No[1]	Yes
Cladribine	No	No
Cyclophosphamide	No	No
Cytarabine	No	No
Dacarbazine	No	Yes
Dactinomycin	Yes	No
Daunorubicin	Yes	No
Daunorubicin liposome	No	No
Denileukin diftitox	No	Yes
Dexrazoxane	No	Yes
Docetaxel	No	No
Doxorubicin	Yes	Yes
Doxorubicin liposome	No	Yes
Epirubicin	Yes	No
Etoposide	No[2]	Yes
Floxuridine	No	No
Fludarabine	No	No
5-Fluorouracil	No	No
Gemcitabine	No	No
Idarubicin	Yes	No
Ifosfamide	No	Yes
Irinotecan	No	No
Mechlorethamine	Yes	No
Methotrexate	No	No
Mitomycin-C	Yes	No
Mitoxantrone	Yes[3]	No

Table 10. (cont)

Drug	*VESICANT*	*IRRITANT*
Oxaliplatin	No	No
Paclitaxel	Yes[4]	No
Pentostatin	No	No
Rituximab	No	No
Streptozocin	Yes	Yes
Thiotepa	No	Yes
Topotecan	No	No
Trastuzumab	No	No
Vinblastine	Yes	No
Vincristine	Yes	No
Vindesine	Yes	No
Vinorelbine	Yes	Yes

[1] Cisplatin is vesicant if > 20 mL of 0.5 mg/mL solution extravasates.

[2] Treatment is necessary only if a large volume of concentrated solution extravasates.

[3] Ulceration rarely occurs unless concentrated doses infiltrate.

[4] Weak vesicant.

Irritant

- Capable of inducing a local inflammatory reaction.
- Tenderness along the vein with burning and erythema.
- Intact blood return.
- Short-term injury that does not lead to tissue injury or necrosis.

Vesicant

- Infiltration of drug into surrounding tissue causes erythema and blistering.
- Symptoms may be delayed for up to 6–12 hours after drug extravasation. Complaints of pruritus are common in the absence of pain.
- Severe necrosis with involvement of tendons and joints may occur.
- Absent blood return.
- Level of tissue damage depends on the vesicant potential of the drug, the volume and concentration of drug infiltrated, the site of infiltration, the length of drug exposure, and the immediate measures taken once drug extravasation occurs.

Table 11. Classification of Teratogenic Potential and Use-in-Pregnancy for Chemotherapy Agents

Pregnancy Category A. Controlled studies show no risk in pregnancy.

Controlled studies in pregnant women have not shown an increased risk of fetal abnormalities when the drug is administered during pregnancy. The possibility of fetal harm appears remote when the drug is used during pregnancy.

Pregnancy Category B. No evidence of risk in pregnancy.

(a) Controlled studies in animals have shown that the drug poses a risk to the fetus. However, studies in pregnant women have failed to show such a risk.

(b) Controlled studies in animals do not show evidence of impaired fertility or harm to the fetus. However, similar studies have not been performed in humans. Because animal studies are not entirely predictive of human response, the drug should be used during pregnancy only if clearly needed.

Pregnancy Category C. Risk in pregnancy cannot be ruled out.

Controlled studies either have not been conducted in animals or show that the drug is teratogenic or has an embryocidal effect and/or other adverse effect in animals. However, there are no adequate and well-controlled studies in pregnant women. The drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Pregnancy Category D. Clear evidence of risk in pregnancy.

The drug can cause fetal harm when administered to a pregnant woman. If the drug is used during pregnancy, or if a patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to the fetus. However, the potential benefits of treatment may outweigh any potential risk.

Pregnancy Category X. Absolutely contraindicated in pregnancy.

The drug has been shown to cause fetal harm when administered to a pregnant woman. The drug is absolutely contraindicated in women who are or may become pregnant. If this drug is used during pregnancy, or if a patient becomes pregnant while taking this drug, the patient should be informed of the potential hazard to the fetus. The potential risk, in this case, outweighs any potential benefit from treatment.

4

Common Chemotherapy Regimens in Clinical Practice

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This chapter presents some of the common combination regimens as well as selected single-agent regimens for solid tumors and hematologic malignancies. They are organized alphabetically by the specific cancer type. In each case, the regimens selected are based on the published literature and are used in clinical practice in the medical oncology community. It should be emphasized that not all of the drugs and dosages in the regimens have been officially approved by the Food and Drug Administration (FDA) for the treatment of a particular tumor. This chapter should serve as a quick reference for physicians and health care providers actively engaged in the practice of cancer treatment and provides several options for treating an individual tumor type. It is not intended to be an all-inclusive review of current treatments or to endorse and/or prioritize any particular combination or single-agent regimen.

It is important to emphasize that the reader should carefully review the original reference for each of the regimens cited to confirm the specific doses and schedules and to check the complete prescribing information contained within the package insert for each agent.

While considerable efforts have been made to ensure the accuracy of the regimens presented, printing and/or typographical errors may have been made in the preparation of this book. As a result, no liability can be assumed for their use. Moreover, the reader should be reminded that several variations in combination and single-agent regimens exist based on institutional and/or individual experience. Additionally, modifications in

dose and schedule may be required according to performance status, baseline hepatic and/or renal function, toxicity, and individual patient response.

ANAL CANCER

5-Fluorouracil + Mitomycin-C + Radiation Therapy (Wayne State regimen)

5-Fluorouracil:	1,000 mg/m²/day IV continuous infusion on days 1–4 and 29–32
Mitomycin-C:	15 mg/m² IV on day 1
Radiation therapy:	200 cGy/day on days 1–5, 8–12, and 5–19 (total dose, 3,000 cGy)

Chemotherapy is given concurrently with radiation therapy (1).

5-Fluorouracil + Mitomycin-C + Radiation Therapy (EORTC regimen)

5-Fluorouracil:	750 mg/m²/day IV continuous infusion on days 1–5 and 29–33
Mitomycin-C:	15 mg/m² IV on day 1
Radiation therapy:	180 cGy/day over 5 week period (total dose, 4,500 cGy)

Chemotherapy is given concurrently with radiation therapy. If partial or complete response, a boost of 1,500–2,000 cGy is given (2).

5-Fluorouracil + Cisplatin + Radiation Therapy (MD Anderson regimen)

5-Fluorouracil:	250 mg/m²/day IV continuous infusion on days 1–5 of each week of radiation therapy
Cisplatin:	4 mg/m²/day IV continuous infusion on days 1–5 of each week of radiation therapy
Radiation therapy:	Total dose, 5,500 cGy over 6 weeks

Chemotherapy is given concurrently with radiation therapy (3).

Metastatic Disease and/or Salvage Chemotherapy

5-Fluorouracil + Cisplatin

5-Fluorouracil:	1,000 mg/m²/day IV continuous infusion on days 1–5
Cisplatin:	100 mg/m² IV on day 2

Repeat cycle every 21–28 days (4).

BILIARY TRACT CANCER

Combination Regimens

Gemcitabine + Cisplatin

Gemcitabine: 1,250 mg/m^2 IV on days 1 and 8

Cisplatin: 75 mg/m^2 IV on day 1

Repeat cycle every 21 days (5).

Gemcitabine + Capecitabine

Gemcitabine: 1,000 mg/m^2 IV on days 1, 8

Capecitabine: 650 mg/m^2 IV on days 1–14

Repeat cycle every 21 days (6).

BLADDER CANCER

Combination Regimens

ITP

Ifosfamide: 1,500 mg/m^2 IV on days 1–3

Paclitaxel: 200 mg/m^2 IV over 3 hours on day 1

Cisplatin: 70 mg/m^2 IV on day 1

Repeat cycle every 21 days (7). G-CSF support is recommended. Regimen can also be administered every 28 days.

Gemcitabine + Cisplatin

Gemcitabine: 1,000 mg/m^2 IV on days 1, 8, and 15

Cisplatin: 75 mg/m^2 IV on day 1

Repeat cycle every 28 days (8).

MVAC

Methotrexate: 30 mg/m^2 IV on days 1, 15, and 22

Vinblastine: 3 mg/m^2 IV on days 2, 15, and 22

Doxorubicin: 30 mg/m^2 IV on day 2

Cisplatin: 70 mg/m^2 IV on day 2

Repeat cycle every 28 days (9).

CMV

Cisplatin:	100 mg/m² IV on day 2 (give 12 hours after methotrexate)
Methotrexate:	30 mg/m² IV on days 1 and 8
Vinblastine:	4 mg/m² IV on days 1 and 8

Repeat cycle every 21 days (10).

CISCA

Cyclophosphamide:	650 mg/m² IV on day 1
Doxorubicin:	50 mg/m² IV on day 1
Cisplatin:	100 mg/m² IV on day 2

Repeat cycle every 21–28 days (11).

Paclitaxel + Carboplatin

Paclitaxel:	225 mg/m² IV over 3 hours on day 1
Carboplatin:	AUC of 6, IV on day 1, given 15 minutes after paclitaxel

Repeat cycle every 21 days (12).

CAP

Cyclophosphamide:	400 mg/m² IV on day 1
Doxorubicin:	40 mg/m² IV on day 1
Cisplatin:	75 mg/m² IV on day 1

Repeat cycle every 21 days (13).

CMV + Radiation Therapy

Cisplatin:	70 mg/m² IV on day 2
Methotrexate:	30 mg/m² IV on days 1, 15, and 22
Vinblastine:	3 mg/m² IV on days 2, 15, and 22

Repeat cycle every 28 days for 2 cycles (14). Radiation therapy to be given after 2 cycles of induction chemotherapy at a total dose of 45 cGy in 180 cGy fractions combined with cisplatin 70 mg/m² IV on days 1 and 2 of radiation therapy.

Single-Agent Regimens

Gemcitabine

Gemcitabine: 1,200 mg/m^2 IV on days 1, 8, and 15

Repeat cycle every 28 days (15).

Paclitaxel

Paclitaxel: 250 mg/m^2 IV over 24 hours on day 1

Repeat cycle every 21 days (16).
or

Paclitaxel: 80 mg/m^2 IV weekly for 3 weeks

Repeat cycle every 4 weeks (17).

BRAIN CANCER

Adjuvant Therapy

Combination Regimens

Temozolomide + Radiation Therapy

Radiation therapy: 200 cGy/day for 5 days per week for total of 6 weeks

Temozolomide: 75 mg/m^2 PO for 6 weeks with radiation therapy, followed by 150 mg/m^2 PO on days 1–5

Repeat cycle every 28 days (18). If well tolerated, can increase dose to 200 mg/m^2.

PCV

Procarbazine: 60 mg/m^2 PO on days 8–21

Lomustine: 130 mg/m^2 PO on day 1

Vincristine: 1.4 mg/m^2 IV on days 8 and 29

Repeat cycle every 8 weeks for 6 cycles (19).

Single-Agent Regimens

BCNU

BCNU: 220 mg/m^2 IV on day 1

Repeat cycle every 6–8 weeks for 1 year (20).
or

BCNU: 75–100 mg/m² IV on days 1 and 2

Repeat cycle every 6–8 weeks (20).

Advanced Disease

Combination Regimens

PCV

Procarbazine: 75 mg/m² PO on days 8–21

Lomustine: 130 mg/m² PO on day 1

Vincristine: 1.4 mg/m² IV on days 8 and 29

Repeat cycle every 8 weeks (21).

Single-Agent Regimens

BCNU

BCNU: 200 mg/m² IV on day 1

Repeat cycle every 6–8 weeks (21).

Procarbazine

Procarbazine: 150 mg/m² PO daily divided into 3 doses

Repeat daily (22).

Temozolomide

Temozolomide: 150 mg/m² PO on days 1–5

Repeat cycle every 28 days (23). If well tolerated, can increase dose to 200 mg/m².

Irinotecan

Irinotecan: 350 mg/m² IV over 90 min on day 1

Repeat cycle every 3 weeks (24).
or

Irinotecan: 125 mg/m² IV weekly for 4 weeks

Repeat cycle every 6 weeks (25).

BREAST CANCER

Neoadjuvant Therapy

Combination Regimens

ACT

Doxorubicin: 60 mg/m² IV on day 1

Cyclophosphamide: 600 mg/m² IV on day 1

Docetaxel: 100 mg/m² IV on day 1

Repeat cycle every 21 days for a total of 4 cycles, followed by surgery (26).

Adjuvant Therapy

Combination Regimens

AC

Doxorubicin: 60 mg/m² IV on day 1

Cyclophosphamide: 600 mg/m² IV on day 1

Repeat cycle every 21 days for a total of 4 cycles (27).

AC→T

Doxorubicin: 60 mg/m² IV on day 1

Cyclophosphamide: 600 mg/m² IV on day 1

Repeat cycle every 21 days for a total of 4 cycles, followed by

Paclitaxel: 175 mg/m² IV on day 1

Repeat cycle every 21 days for a total of 4 cycles (28).

AC→T + Trastuzumab

Doxorubicin: 60 mg/m² IV on day 1

Cyclophosphamide: 600 mg/m² IV on day 1

Repeat cycle every 21 days for a total of 4 cycles, followed by

Paclitaxel: 80 mg/m² IV over 1 hour on day 1

Trastuzumab: 4 mg/kg IV loading dose, then 2 mg/kg IV weekly

Repeat weekly for 12 weeks, followed by

Trastuzumab: 2 mg/kg IV weekly

Repeat weekly for 40 weeks (29).

A→ T→ C (dose-dense therapy)

Doxorubicin: 60 mg/m² IV on day 1

Repeat cycle every 2 weeks for 4 cycles, followed by

Paclitaxel: 175 mg/m² IV on day 1

Repeat cycle every 2 weeks for 4 cycles, followed by

Cyclophosphamide: 600 mg/m² IV on day 1

Repeat cycle every 2 weeks for 4 cycles.

Administer filgrastim 5 μg/kg SC on days 3–10 of each weekly cycle (30).

CAF

Cyclophosphamide: 600 mg/m² IV on day 1

Doxorubicin: 60 mg/m² IV on day 1

5-Fluorouracil: 600 mg/m² IV on day 1

Repeat cycle every 28 days for a total of 4 cycles (31).

or

Cyclophosphamide: 100 mg/m² PO on days 1–14

Doxorubicin: 30 mg/m² IV on days 1 and 8

5-Fluorouracil: 500 mg/m² IV on days 1 and 8

Repeat cycle every 28 days for a total of 6 cycles (32).

CMF (Bonadonna regimen)

Cyclophosphamide: 100 mg/m²/day PO on days 1–14

Methotrexate: 40 mg/m² IV on days 1 and 8

5-Fluorouracil: 600 mg/m² IV on days 1 and 8

Repeat cycle every 28 days for a total of 6 cycles (33).

CMF (IV regimen)

Cyclophosphamide: 600 mg/m² IV on day 1

Methotrexate: 40 mg/m² IV on day 1

5-Fluorouracil: 600 mg/m² IV on day 1

Repeat cycle every 21 days for a total of 6 cycles (34).

Doxorubicin + CMF

Doxorubicin: 75 mg/m² IV on day 1

Repeat cycle every 21 days for a total of 4 cycles, then

Cyclophosphamide: 600 mg/m² IV on day 1

Methotrexate: 40 mg/m² IV on day 1

5-Fluorouracil: 600 mg/m² IV on day 1

Repeat cycle every 21 days for a total of 8 cycles (35).

FEC

5-Fluorouracil: 500 mg/m² IV on day 1

Epirubicin: 100 mg/m² IV on day 1

Cyclophosphamide: 500 mg/m² IV on day 1

Repeat cycle every 21 days for a total of 6 cycles (36).

CMFP

Cyclophosphamide: 100 mg/m² PO on days 1–14

Methotrexate: 40 mg/m² IV on days 1 and 8

5-Fluorouracil: 600 mg/m² IV on days 1 and 8

Prednisone: 20 mg PO qid on days 1–7

Repeat cycle every 28 days (37).

Single-Agent Regimens

Tamoxifen

Tamoxifen: 20 mg PO daily

Repeat daily for 5 years in patients with ER+ tumors or ER status unknown (38).

Anastrozole

Anastrozole: 1 mg PO daily

Repeat daily for 5 years in patients with ER+ tumors or ER status unknown (39).

Tamoxifen + Letrozole (40)

Tamoxifen: 20 mg PO daily for 5 years, followed by

Letrozole: 2.5 mg PO daily for 5 years

Tamoxifen + Exemestane (41)

Tamoxifen: 20 mg PO daily for 2–3 years, followed by

Exemestane: 25 mg PO daily for the remainder of 5 years

Metastatic Disease

Combination Regimens

AC

Doxorubicin: 60 mg/m^2 IV on day 1

Cyclophosphamide: 600 mg/m^2 IV on day 1

Repeat cycle every 21 days (27).

AT

Doxorubicin: 50 mg/m^2 IV on day 1

Paclitaxel: 150 mg/m^2 IV over 24 hours on day 1

Repeat cycle every 21 days (42).
or

Doxorubicin: 60 mg/m^2 IV on day 1

Repeat cycle every 21 days up to a maximum of 8 cycles, followed by

Paclitaxel: 175 mg/m^2 IV on day 1

Repeat cycle every 21 days until disease progression (42).
or

Paclitaxel: 175 mg/m^2 IV on day 1

Repeat cycle every 21 days until disease progression, followed by

Doxorubicin: 60 mg/m^2 IV on day 1

Repeat cycle every 21 days up to a maximum of 8 cycles (42).

CAF

Cyclophosphamide: 600 mg/m^2 IV on day 1

Doxorubicin: 60 mg/m^2 IV on day 1

5-Fluorouracil: 600 mg/m² IV on day 1

Repeat cycle every 21 days (31).

CEF

Cyclophosphamide: 75 mg/m²/day PO on days 1–14

Epirubicin: 60 mg/m² IV on days 1 and 8

5-Fluorouracil: 500 mg/m² IV on days 1 and 8

Repeat cycle every 28 days (43).

CMF (Bonadonna regimen)

Cyclophosphamide: 100 mg/m²/day PO on days 1–14

Methotrexate: 40 mg/m² IV on days 1 and 8

5-Fluorouracil: 500 mg/m² IV on days 1 and 8

Repeat cycle every 28 days (33).

CMF—IV Bolus

Cyclophosphamide: 600 mg/m² IV on day 1

Methotrexate: 40 mg/m² IV on day 1

5-Fluorouracil: 600 mg/m² IV on day 1

Repeat cycle every 21 days (34).

Capecitabine + Docetaxel (XT)

Capecitabine: 1,250 mg/m² PO bid on days 1–14

Docetaxel: 75 mg/m² IV on day 1

Repeat cycle every 21 days (44). May decrease dose of capecitabine to 850–1,000 mg/m² PO bid on days 1–14 to reduce the risk of toxicity without compromising clinical efficacy.

Capecitabine + Paclitaxel (XP)

Capecitabine: 825 mg/m² PO bid on days 1–14

Paclitaxel: 175 mg/m² IV on day 1

Repeat cycle every 21 days (45).

Capecitabine + Navelbine (XN)

Capecitabine: 1,000 mg/m² PO bid on days 1–14

Navelbine:	25 mg/m² IV on days 1 and 8

Repeat cycle every 21 days (45).

Docetaxel + Doxorubicin

Docetaxel:	75 mg/m² IV on day 1
Doxorubicin:	50 mg/m² IV on day 1

Repeat cycle every 21 days (46).

FEC-100

5-Fluorouracil:	500 mg/m² IV on day 1
Epirubicin:	100 mg/m² IV on day 1
Cyclophosphamide:	500 mg/m² IV on day 1

Repeat cycle every 21 days (47).

Paclitaxel + Vinorelbine

Paclitaxel:	135 mg/m² IV over 3 hours on day 1, starting 1 hour after vinorelbine
Vinorelbine:	30 mg/m² IV over 20 minutes on days 1 and 8

Repeat cycle every 28 days (48).

Vinorelbine + Doxorubicin

Vinorelbine:	25 mg/m² IV on days 1 and 8
Doxorubicin:	50 mg/m² IV on day 1

Repeat cycle every 21 days (49).

Trastuzumab-Paclitaxel

Trastuzumab:	4 mg/kg IV loading dose, then 2 mg/kg weekly
Paclitaxel:	175 mg/m² IV over 3 hours on day 1

Repeat cycle every 21 days (50).
or

Trastuzumab:	4 mg/kg IV loading dose, then 2 mg/kg weekly
Paclitaxel:	80 mg/m² IV weekly

Repeat cycle every 4 weeks (51).

Trastuzumab-Docetaxel

Trastuzumab:	4 mg/kg IV loading dose, then 2 mg/kg IV on days 8 and 15
Docetaxel:	35 mg/m^2 IV on days 1, 8, and 15

The first cycle is administered weekly for 3 weeks, with 1 week rest. For subsequent cycles,

Trastuzumab:	2 mg/kg IV weekly
Docetaxel:	35 mg/m^2 IV weekly

Repeat cycle every 4 weeks (52).

Gemcitabine + Paclitaxel

Gemcitabine:	1,250 mg/m^2 IV on days 1 and 8
Paclitaxel:	175 mg/m^2 IV on day 1

Repeat cycle every 21 days (53).

Carboplatin + Paclitaxel

Carboplatin:	AUC of 6, IV on day 1
Paclitaxel:	200 mg/m^2 IV over 3 hours on day 1

Repeat cycle every 21 days (54).

Carboplatin + Docetaxel

Carboplatin:	AUC of 6, IV on day 1
Docetaxel:	75 mg/m^2 IV on day 1

Repeat cycle every 21 days (55).

Mitomycin + Vinblastine

Mitomycin:	20 mg/m^2 IV on day 1
Vinblastine:	1.4–2 mg/m^2 IV continuous infusion on days 1–5

Repeat cycle every 6–8 weeks (56).

Single-Agent Regimens

Tamoxifen

Tamoxifen:	20 mg PO daily (57)

Toremifene citrate

Toremifene: 60 mg PO daily (58)

Exemestane

Exemestane: 25 mg PO daily (59)

Anastrozole

Anastrozole: 1 mg PO daily (60)

Letrozole

Letrozole: 2.5 mg PO daily (61)

Fulvestrant

Fulvestrant: 250 mg IM on day 1

Repeat injection every month (62).

Megestrol

Megestrol: 40 mg PO qid (63)

Trastuzumab

Trastuzumab: 4 mg/kg IV loading dose, then 2 mg/kg IV weekly

Repeat cycle weekly for a total of 10 weeks. In the absence of disease progression, continue weekly maintenance dose of 2 mg/kg (64).
or

Trastuzumab: 8 mg/kg IV loading dose, then 6 mg/kg IV every 3 weeks

Continue 6 mg/kg every 3 weeks until disease progression (64a).

Capecitabine

Capecitabine: 1,250 mg/m^2 PO bid for 2 weeks followed by 1 week rest period

Repeat cycle every 21 days (65). May decrease dose to 850–1,000 mg/m^2 PO bid on days 1–14 to reduce the risk of toxicity without compromising clinical efficacy.

Docetaxel

Docetaxel: 100 mg/m^2 IV on day 1

Repeat cycle every 21 days (66).
or

Docetaxel: 35–40 mg/m^2 IV weekly for 6 weeks

Repeat cycle every 8 weeks (67).

Paclitaxel

Paclitaxel: 175 mg/m^2 IV over 3 hours on day 1

Repeat cycle every 21 days (68).
or

Paclitaxel: 80–100 mg/m^2 IV weekly for 3 weeks

Repeat cycle every 4 weeks (69).

Vinorelbine

Vinorelbine: 30 mg/m^2 IV on day 1

Repeat cycle every 7 days (70).

Doxorubicin

Doxorubicin: 20 mg/m^2 IV on day 1

Repeat cycle every 7 days (71).

Gemcitabine

Gemcitabine: 725 mg/m^2 IV weekly for 3 weeks

Repeat cycle every 28 days (72).

Liposomal Doxorubicin

Liposomal
Doxorubicin: 45–60 mg/m^2 IV on day 1

Repeat cycle every 21–28 days (73).

Abraxane

Abraxane: 260 mg/m^2 IV on day 1

Repeat cycle every 21 days (74).
or

Abraxane: 125 mg/m^2 IV on days 1, 8, and 15

Repeat cycle every 28 days (75).

CANCER OF UNKNOWN PRIMARY

PCE

Paclitaxel:	200 mg/m² IV over 1 hour on day 1
Carboplatin:	AUC of 6, IV on day 1
Etoposide:	50 mg alternating with 100 mg PO on days 1–10

Repeat cycle every 21 days (76).

EP

Etoposide:	100 mg/m² IV on days 1–5
Cisplatin:	100 mg/m² IV on day 1

Repeat cycle every 21 days (77).

PEB

Cisplatin:	20 mg/m² IV on days 1–5
Etoposide:	100 mg/m² IV on days 1–5
Bleomycin:	30 units IV on days 1, 8, and 15

Repeat cycle every 21 days (78).

GCP

Gemcitabine:	1,000 mg/m² IV on days 1 and 8
Carboplatin:	AUC of 5, IV on day 1
Paclitaxel:	200 mg/m² IV on day 1

Repeat cycle every 21 days for 4 cycles (79). This is to be followed by paclitaxel at 70 mg/m² IV every week for 6 weeks with a 2-week rest. Repeat for a total of 3 cycles.

CARCINOID TUMORS

Combination Regimens

5-Fluorouracil + Streptozocin

5-Fluorouracil:	400 mg/m²/day IV on days 1–5
Streptozocin:	500 mg/m²/day IV on days 1–5

Repeat cycle every 6 weeks (80).

Doxorubicin + Streptozocin

Doxorubicin: 50 mg/m² IV on days 1 and 22

Streptozocin: 500 mg/m²/day IV on days 1–5

Repeat cycle every 6 weeks (80).

Cisplatin + Etoposide

Cisplatin: 45 mg/m²/day IV continuous infusion on days 2 and 3

Etoposide: 130 mg/m²/day IV continuous infusion on days 1–3

Repeat cycle every 21 days (81).

Single-Agent Regimens

Octreotide

Octreotide: 150–250 μg SC tid

Continue until disease progression (82).

CERVICAL CANCER

Combination Regimens

Cisplatin + Radiation Therapy

Radiation therapy: 1.8 to 2 Gy per fraction (total dose, 45 Gy)

Cisplatin: 40 mg/m² IV weekly (maximal dose, 70 mg per week)

Cisplatin is given 4 hours before radiation therapy on weeks 1–6 (83).

Paclitaxel + Cisplatin

Paclitaxel: 135 mg/m² IV over 24 hours on day 1

Cisplatin: 75 mg/m² IV on day 2

Repeat cycle every 21 days (84).

Cisplatin + Topotecan

Cisplatin: 50 mg/m² IV on day 1

Topotecan: 0.75 mg/m²/day IV on days 1–3

Repeat cycle every 21 days (85).

BIP

Bleomycin:	30 U IV over 24 hours on day 1
Ifosfamide:	5,000 mg/m^2 IV over 24 hours on day 2
Mesna:	6,000 mg/m^2 IV over 36 hours on day 2
Cisplatin:	50 mg/m^2 IV on day 2

Repeat cycle every 21 days (86).

BIC

Bleomycin:	30 U IV on day 1
Ifosfamide:	2,000 mg/m^2 IV on days 1–3
Mesna:	400 mg/m^2 IV, 15 minutes before ifosfamide dose, then 400 mg/m^2 IV at 4 and 8 hours following ifosfamide
Carboplatin:	200 mg/m^2 IV on day 1

Repeat cycle every 21 days (87).

Cisplatin + 5-Fluorouracil

Cisplatin:	75 mg/m^2 IV on day 1
5-Fluorouracil:	1,000 mg/m^2 IV continuous infusion on days 2–5

Repeat cycle every 21 days (88).

Cisplatin + Vinorelbine

Cisplatin:	80 mg/m^2 IV on day 1
Vinorelbine:	25 mg/m^2 IV on days 1 and 8

Repeat cycle every 21 days (89).

Cisplatin + Irinotecan

Cisplatin:	60 mg/m^2 IV on day 1
Irinotecan:	60 mg/m^2 IV on days 1, 8, and 15

Repeat cycle every 28 days (90).

Single-Agent Regimens

Cisplatin

Cisplatin: 50–100 mg/m² IV on day 1

Repeat cycle every 21 days (91).

Docetaxel

Docetaxel: 100 mg/m² IV on day 1

Repeat cycle every 21 days (92).

Paclitaxel

Paclitaxel: 175 mg/m² IV over 3 hours on day 1

Repeat cycle every 21 days (93).

Irinotecan

Irinotecan: 125 mg/m² IV weekly for 4 weeks

Repeat cycle every 6 weeks (94).

Vinorelbine

Vinorelbine: 30 mg/m² IV weekly

Repeat cycle every week up to 12 cycles, to be followed by surgery or radiotherapy (95).

Topotecan

Topotecan: 1.5 mg/m²/day on days 1–5

Repeat cycle every 21 days (96).

COLORECTAL CANCER

Neoadjuvant Combined Modality Therapy for Rectal Cancer

Combination Regimens

5-Fluorouracil + Radiation Therapy (German AIO regimen)

5-Fluorouracil: 1,000 mg/m²/day IV continuous infusion on days 1–5

Repeat infusional 5-FU on weeks 1 and 5.

Radiation therapy:	180 cGy/day for 5 days per week (total dose, 5,040 cGy)

Followed by surgical resection and then adjuvant chemotherapy with 5-FU at 500 mg/m² IV for 5 days every 28 days for a total of 4 cycles. (97).

Capecitabine + Radiation Therapy

Capecitabine:	825 mg/m² PO bid throughout the entire course of radiation therapy or 900–1,000 mg/m² PO bid on days 1–5 of each week of radiation therapy
Radiation therapy:	180 cGy/day for 5 days per week (total dose, 5,040 cGy)

Followed by surgical resection and then adjuvant chemotherapy with 5-FU or 5-FU/LV for a total of 4 cycles (98).

Adjuvant Therapy

5-Fluorouracil + Leucovorin (Mayo Clinic schedule)

5-Fluorouracil:	425 mg/m² IV on days 1–5
Leucovorin:	20 mg/m² IV on days 1–5, administered before 5-fluorouracil

Repeat cycle every 4–5 weeks for a total of 6 cycles (99).

5-Fluorouracil + Leucovorin (weekly schedule, high dose)

5-Fluorouracil:	500 mg/m² IV weekly for 6 weeks
Leucovorin:	500 mg/m² IV over 2 hours weekly for 6 weeks, administered before 5-fluorouracil

Repeat cycle every 8 weeks for a total of 4 cycles (32 weeks total) (100).

5-Fluorouracil + Leucovorin (weekly schedule, low dose)

5-Fluorouracil:	500 mg/m² IV weekly for 6 weeks
Leucovorin:	20 mg/m² IV weekly for 6 weeks, administered before 5-fluorouracil

Repeat cycle every 8 weeks for a total of 4 or 6 cycles (32 or 48 weeks total) (101).

Oxaliplatin + 5-Fluorouracil + Leucovorin (FOLFOX4)

Oxaliplatin:	85 mg/m² IV on day 1
5-Fluorouracil:	400 mg/m² IV bolus, followed by 600 mg/m² IV continuous infusion for 22 hours on days 1 and 2
Leucovorin:	200 mg/m² IV on days 1 and 2 as a 2-hour infusion before 5-fluorouracil

Repeat cycle every 2 weeks for a total of 12 cycles (102).

Capecitabine

Capecitabine:	1,250 mg/m² PO bid on days 1–14

Repeat cycle every 21 days for a total of 8 cycles (103). Dose may be decreased to 850–1,000 mg/m² PO bid on days 1–14 to reduce the risk of toxicity without compromising clinical efficacy.

Metastatic Disease

Combination Regimens

Irinotecan + 5-Fluorouracil + Leucovorin (IFL Saltz regimen)

Irinotecan:	125 mg/m² IV over 90 minutes weekly for 4 weeks
5-Fluorouracil:	500 mg/m² IV weekly for 4 weeks
Leucovorin:	20 mg/m² IV weekly for 4 weeks

Repeat cycle every 6 weeks (104).

Irinotecan + 5-Fluorouracil + Leucovorin (IFL Saltz regimen) + Bevacizumab (BV)

Irinotecan:	125 mg/m² IV over 90 minutes weekly for 4 weeks
5-Fluorouracil:	500 mg/m² IV weekly for 4 weeks
Leucovorin:	20 mg/m² IV weekly for 4 weeks
Bevacizumab:	5 mg/kg IV every 2 weeks

Repeat cycle every 6 weeks (105).

Irinotecan + 5-Fluorouracil + Leucovorin (Modified IFL Saltz regimen)

Irinotecan:	125 mg/m² IV over 90 minutes weekly for 2 weeks

5-Fluorouracil:	500 mg/m² IV weekly for 2 weeks
Leucovorin:	20 mg/m² IV weekly for 2 weeks

Repeat cycle every 3 weeks (106).

IFL Douillard Regimen

Irinotecan:	180 mg/m² IV on day 1
5-Fluorouracil:	400 mg/m² IV bolus, followed by 600 mg/m² IV continuous infusion for 22 hours on days 1 and 2
Leucovorin:	200 mg/m² IV on days 1 and 2 as a 2-hour infusion prior to 5-fluorouracil

Repeat cycle every 2 weeks (107).

IFL FOLFIRI Regimen

Irinotecan:	180 mg/m² IV on day 1
5-Fluorouracil:	400 mg/m² IV bolus on day 1, followed by 2,400 mg/m² IV continuous infusion for 46 hours
Leucovorin:	200 mg/m² IV on day 1 as a 2-hour infusion prior to 5-fluorouracil

Repeat cycle every 2 weeks (108).

Oxaliplatin + 5-Fluorouracil + Leucovorin (FOLFOX4)

Oxaliplatin:	85 mg/m² IV on day 1
5-Fluorouracil:	400 mg/m² IV bolus, followed by 600 mg/m² IV continuous infusion for 22 hours on days 1 and 2
Leucovorin:	200 mg/m² IV on days 1 and 2 as a 2-hour infusion before 5-fluorouracil

Repeat cycle every 2 weeks (109).

Oxaliplatin + 5-Fluorouracil + Leucovorin (FOLFOX6)

Oxaliplatin:	100 mg/m² IV on day 1
5-Fluorouracil:	400 mg/m² IV bolus on day 1, followed by 2,400 mg/m² IV continuous infusion for 46 hours

Leucovorin:	400 mg/m² IV on day 1 as a 2-hour infusion before 5-fluorouracil

Repeat cycle every 2 weeks (110).

Oxaliplatin + 5-Fluorouracil + Leucovorin (FOLFOX7)

Oxaliplatin:	130 mg/m² IV on day 1
5-Fluorouracil:	2,400 mg/m² IV continuous infusion on days 1 and 2 for 46 hours
Leucovorin:	400 mg/m² IV on day 1 as a 2-hour infusion before 5-fluorouracil

Repeat cycle every 2 weeks (111).

Cetuximab + Irinotecan

Cetuximab:	400 mg/m² IV loading dose, then 250 mg/m² IV weekly
Irinotecan:	350 mg/m² IV on day 1

Repeat cycle every 21 days (112).

Capecitabine + Oxaliplatin (XELOX)

Capecitabine:	1,000 mg/m² PO bid on days 1–14
Oxaliplatin:	130 mg/m² IV on day 1

Repeat cycle every 21 days (96). May decrease dose of capecitabine to 850 mg/m² PO bid and dose of oxaliplatin to 100 mg/m² IV to reduce the risk of toxicity without compromising clinical efficacy.
or

Capecitabine:	1,750 mg/m² PO bid on days 1–7
Oxaliplatin:	85 mg/m² IV on day 1

Repeat cycle every 14 days (113).

Capecitabine + Irinotecan (XELIRI)

Capecitabine:	1,000 mg/m² PO bid on days 1–14
Irinotecan:	250 mg/m² IV on day 1

Repeat cycle every 21 days (114). May decrease dose of capecitabine to 850 mg/m² PO bid and dose of irinotecan to 200 mg/m² IV to reduce the risk of toxicity without compromising clinical efficacy.

Oxaliplatin + Irinotecan (IROX regimen)

Oxaliplatin: 85 mg/m² IV on day 1

Irinotecan: 200 mg/m² IV on day 1

Repeat cycle every 3 weeks (115).

5-Fluorouracil + Leucovorin (Mayo Clinic schedule)

5-Fluorouracil: 425 mg/m² IV on days 1–5

Leucovorin: 20 mg/m² IV on days 1–5, administered before 5-fluorouracil

Repeat cycle every 4–5 weeks (116).

5-Fluorouracil + Leucovorin (Roswell Park schedule, high dose)

5-Fluorouracil: 500 mg/m² IV weekly for 6 weeks

Leucovorin: 500 mg/m² IV weekly for 6 weeks, administered before 5-fluorouracil

Repeat cycle every 8 weeks (117).

5-Fluorouracil + Leucovorin + Bevacizumab

5-Fluorouracil: 500 mg/m² IV weekly for 6 weeks

Leucovorin: 500 mg/m² IV weekly for 6 weeks, administered before 5-fluorouracil

Bevacizumab: 5 mg/kg IV every 2 weeks

Repeat cycle every 8 weeks (118).

5-Fluorouracil + Leucovorin (German schedule, low dose)

5-Fluorouracil: 600 mg/m² IV weekly for 6 weeks

Leucovorin: 20 mg/m² IV weekly for 6 weeks, administered before 5-fluorouracil

Repeat cycle every 8 weeks following a 2-week rest period (119).

5-Fluorouracil + Leucovorin (de Gramont regimen)

5-Fluorouracil: 400 mg/m² IV and then 600 mg/m² IV for 22 hours on days 1 and 2

Leucovorin: 200 mg/m² IV on days 1 and 2 as a 2-hour infusion before 5-fluorouracil

Repeat cycle every 2 weeks (120).

FOLFOX4 + Bevacizumab

Oxaliplatin:	85 mg/m^2 IV on day 1
5-Fluorouracil:	400 mg/m^2 IV bolus, followed by 600 mg/m^2 IV continuous infusion on days 1 and 2
Leucovorin:	200 mg/m^2 IV on days 1 and 2 as a 2-hour infusion before 5-fluorouracil
Bevacizumab:	10 mg/kg IV every 2 weeks

Repeat cycle every 2 weeks (121).

Capecitabine + Oxaliplatin (XELOX) + Bevacizumab

Capecitabine:	850 mg/m^2 PO bid on days 1–14
Oxaliplatin:	130 mg/m^2 IV on day 1
Bevacizumab:	7.5 mg/kg every 3 weeks

Repeat cycle every 21 days (122).

Hepatic Artery Infusion

Floxuridine

Floxuridine (FUDR):	0.3 mg/kg/day HAI on days 1–14
Dexamethasone:	20 mg HAI on days 1–14
Heparin:	50,000 U HAI on days 1–14

Repeat cycle every 14 days (123).

Single-Agent Regimens

Capecitabine

Capecitabine:	1,250 mg/m^2 PO bid on days 1–14

Repeat cycle every 21 days (124). Dose may be decreased to 850–1,000 mg/m^2 PO bid on days 1–14. This dose reduction may reduce the risk of toxicity without compromising clinical efficacy.

CPT-11 (weekly schedule)

CPT-11:	125 mg/m^2 IV over 90 minutes weekly for 4 weeks

Repeat cycle every 6 weeks (125).
or

CPT-11: 125 mg/m² IV over 90 minutes weekly for 2 weeks

Repeat cycle every 3 weeks.
or

CPT-11: 175 mg/m² IV on days 1 and 10

Repeat cycle every 3 weeks (126).

CPT-11 (monthly schedule)

CPT-11: 350 mg/m² IV on day 1

Repeat cycle every 3 weeks (127).

Cetuximab

Cetuximab: 400 mg/m² IV loading dose, then 250 mg/m² IV weekly

Repeat cycle on a weekly basis (128).

5-Fluorouracil (continuous infusion)

5-Fluorouracil: 2,600 mg/m² IV over 24 hours weekly

Repeat cycle weekly for 4 weeks (129).
or

5-Fluorouracil: 1,000 mg/m²/day IV continuous infusion on days 1–4

Repeat cycle every 21–28 days (130).

ENDOMETRIAL CANCER

Combination Regimens

Paclitaxel and Carboplatin

Paclitaxel: 175 mg/m² IV over 3 hours on day 1

Carboplatin: AUC of 5–7, IV on day 1

Repeat cycle every 28 days (131).

AC

Doxorubicin: 60 mg/m² IV on day 1

Cyclophosphamide: 500 mg/m² IV on day 1

Repeat cycle every 21 days (132).

AP

Doxorubicin: 50 mg/m² IV on day 1

Cisplatin: 50 mg/m² IV on day 1

Repeat cycle every 21 days (133).

Doxorubicin + Paclitaxel

Doxorubicin: 50 mg/m² IV on day 1

Paclitaxel: 150 mg/m² IV on day 1

Repeat cycle every 21 days (134).

Cisplatin + Doxorubicin + Paclitaxel

Cisplatin: 50 mg/m² IV on day 1

Doxorubicin: 45 mg/m² IV on day 1

Paclitaxel: 160 mg/m² IV over 3 hours on day 2

Filgrastim: 5 μg/kg SC on days 3–12

Repeat cycle every 21 days (135).

CAP

Cyclophosphamide: 500 mg/m² IV on day 1

Doxorubicin: 50 mg/m² IV on day 1

Cisplatin: 50 mg/m² IV on day 1

Repeat cycle every 21 days (136).

Single-Agent Regimens

Doxorubicin

Doxorubicin: 60 mg/m² IV on day 1

Repeat cycle every 21 days (137).

Megestrol

Megestrol: 160 mg PO daily

Repeat on a daily basis (138).

Paclitaxel

Paclitaxel: 200 mg/m² IV over 3 hours on day 1

Repeat cycle every 21 days (139). Reduce dose to 175 mg/m² IV for patients with prior pelvic radiation therapy.

Topotecan

Topotecan: 1.0 mg/m²/day IV on days 1–5

Repeat cycle every 21 days (140). Reduce dose to 0.8 mg/m²/day IV on days 1–3 in patients with prior radiation therapy.

ESOPHAGEAL CANCER

Combined Modality Therapy

Combination Regimens

5-Fluorouracil + Cisplatin + Radiation Therapy (Herskovic regimen)

5-Fluorouracil: 1,000 mg/m²/day IV continuous infusion on days 1–4

Cisplatin: 75 mg/m² IV on day 1

Repeat on weeks 1, 5, 8, and 11 (141).

Radiation therapy: 200 cGy/day for 5 days per week (total dose, 3,000 cGy), followed by a boost to the field of 2,000 cGy.

5-Fluorouracil + Cisplatin + Radiation Therapy (Hopkins/Yale regimen)

Preoperative chemoradiation

5-Fluorouracil: 225 mg/m²/day IV continuous infusion on days 1–30

Cisplatin: 20 mg/m²/day IV on days 1–5 and 26–30

Radiation therapy: 200 cGy/day to a total dose of 4,400 cGy

Followed by esophagectomy and then adjuvant chemotherapy in patients who had total gross removal of disease with negative margins.

Adjuvant chemotherapy

Paclitaxel: 135 mg/m² IV for 24 hours on day 1

Cisplatin: 75 mg/m² IV on day 2

Chemotherapy is given concurrently with radiation therapy. Adjuvant chemotherapy is given 8–12 weeks after esophagectomy, and each cycle is given every 21 days for a total of 3 cycles (142).

Metastatic Disease

5-Fluorouracil + Cisplatin

5-Fluorouracil: 1,000 mg/m^2/day IV continuous infusion on days 1–5

Cisplatin: 100 mg/m^2 IV on day 1

Repeat cycle on weeks 1, 5, 8, and 11 (143).

Irinotecan + Cisplatin

Irinotecan: 65 mg/m^2 IV weekly for 4 weeks

Cisplatin: 30 mg/m^2 IV weekly for 4 weeks

Repeat cycle every 6 weeks (144).

Paclitaxel + Cisplatin

Paclitaxel: 200 mg/m^2 IV over 24 hours on day 1

Cisplatin: 75 mg/m^2 IV on day 2

Repeat cycle every 21 days (145). G-CSF support is recommended.

Single-Agent Regimens

Paclitaxel

Paclitaxel: 250 mg/m^2 IV over 24 hours on day 1

Repeat cycle every 21 days (146). G-CSF support is recommended.

GASTRIC CANCER

Adjuvant Therapy

One cycle of chemotherapy is administered as follows:

5-Fluorouracil: 425 mg/m^2 IV on days 1–5

Leucovorin: 20 mg/m^2 IV on days 1–5

Chemoradiotherapy is then started 28 days after the start of the initial cycle of chemotherapy as follows:

Radiation therapy: 180 cGy/day to a total dose of 4,500 cGy, starting on day 28

5-Fluorouracil: 400 mg/m^2 IV on days 1–4 and days 23–25 of radiation therapy

Leucovorin:	20 mg/m² IV on days 1–4 and days 23–25 of radiation therapy

Chemoradiotherapy is followed by 2 cycles of chemotherapy that are given 1 month apart and include (147):

5-Fluorouracil:	425 mg/m² IV on days 1–5
Leucovorin:	20 mg/m² IV on days 1–5

Combination Regimens

DCF

Docetaxel:	75 mg/m² IV on day 1
Cisplatin:	75 mg/m² IV over 1–3 hours on day 1
5-FU:	750 mg/m²/day IV continuous infusion on days 1–5

Repeat cycle every 21 days (148).

CF

Cisplatin:	100 mg/m² IV over 1–3 hours on day 1
5-FU:	1,000 mg/m²/day IV continuous infusion on days 1–5

Repeat cycle every 28 days (148).

EAP

Etoposide:	120 mg/m² IV on days 4–6
Doxorubicin:	20 mg/m² IV on days 1 and 7
Cisplatin:	40 mg/m² IV on days 2 and 8

Repeat cycle every 21–28 days (149).

ECF

Epirubicin:	50 mg/m² IV on day 1
Cisplatin:	60 mg/m² IV on day 1
5-Fluorouracil:	200 mg/m²/day IV continuous infusion for 21 weeks

Repeat cycle every 21 days (150).

ELF

Etoposide:	120 mg/m² IV on days 1–3
Leucovorin:	300 mg/m² IV on days 1–3
5-Fluorouracil:	500 mg/m² IV on days 1–3

Repeat cycle every 21–28 days (151).

IP

Irinotecan:	70 mg/m² IV on days 1 and 15
Cisplatin:	800 mg/m² IV on day 1

Repeat cycle every 28 days (152).

FAM

5-Fluorouracil:	600 mg/m² IV on days 1, 8, 29, and 36
Doxorubicin:	30 mg/m² IV on days 1 and 29
Mitomycin-C:	10 mg/m² IV on day 1

Repeat cycle every 8 weeks (153).

FAMTX

5-Fluorouracil:	1,500 mg/m² IV on day 1, starting 1 hour after MTX
Leucovorin:	15 mg/m² PO every 6 hours for 12 doses, starting 24 hours after MTX
Doxorubicin:	30 mg/m² IV on day 15
Methotrexate:	1,500 mg/m² IV on day 1

Repeat cycle every 28 days (154).

FAP

5-Fluorouracil:	300 mg/m² IV on days 1–5
Doxorubicin:	40 mg/m² IV on day 1
Cisplatin:	60 mg/m² IV on day 1

Repeat cycle every 5 weeks (155).

Docetaxel + Cisplatin

Docetaxel:	85 mg/m² IV on day 1
Cisplatin:	75 mg/m² IV on day 1

Repeat cycle every 21 days (156).

Single-Agent Regimens

5-Fluorouracil

5-Fluorouracil: 500 mg/m² IV on days 1–5

Repeat cycle every 28 days (157).

Docetaxel

Docetaxel: 100 mg/m² IV on day 1

Repeat cycle every 21 days (158).
or

Docetaxel: 36 mg/m² IV weekly for 6 weeks

Repeat cycle every 8 weeks (158).

GASTROINTESTINAL STROMAL TUMOR (GIST)

Single-Agent Regimens

Imatinib

Imatinib: 400 mg/day PO

Continue treatment until disease progression (159). Increase dose to 600 mg/day if no response is seen.

HEAD AND NECK CANCER

Combination Regimens

TIP

Paclitaxel: 175 mg/m² IV over 3 hours on day 1

Ifosfamide: 1,000 mg/m² IV over 2 hours on days 1–3

Mesna: 400 mg/m² IV before ifosfamide and
200 mg/m² IV, 4 hours after ifosfamide

Cisplatin: 60 mg/m² IV on day 1

Repeat cycle every 21–28 days (160).

TPF

Docetaxel: 75 mg/m² IV on day 1

Cisplatin:	75–100 mg/m² IV over 24 hours on day 1
5-Fluorouracil:	1,000 mg/m² over 24 hours on days 1–4

Repeat cycle every 21 days (161).

TIC

Paclitaxel:	175 mg/m² IV over 3 hours on day 1
Ifosfamide:	1,000 mg/m² IV over 2 hours on days 1–3
Mesna:	400 mg/m² IV before ifosfamide and 200 mg/m² IV, 4 hours after ifosfamide
Carboplatin:	AUC of 6, IV on day 1

Repeat cycle every 21–28 days (162).

Paclitaxel + Carboplatin

Paclitaxel:	175 mg/m² IV over 3 hours on day 1
Carboplatin:	AUC of 6, IV on day 1

Repeat cycle every 21 days (163).

Paclitaxel + Cisplatin

Paclitaxel:	175 mg/m² IV over 3 hours on day 1
Cisplatin:	75 mg/m² IV on day 2
G-CSF:	5 μg/kg/day SC on days 4–10

Repeat cycle every 21 days (164).

PF

Cisplatin:	100 mg/m² IV on day 1
5-Fluorouracil:	1,000 mg/m²/day IV continuous infusion on days 1–5

Repeat cycle every 21–28 days (165).

PFL

Cisplatin:	100 mg/m² IV on day 1
5-Fluorouracil:	800 mg/m²/day IV continuous infusion on days 1–5
Leucovorin:	50 mg/m² PO every 6 hours on days 1–5

Repeat cycle every 21 days (166).

PF-Larynx Preservation

Cisplatin:	100 mg/m² IV on day 1
5-Fluorouracil:	1,000 mg/m²/day IV continuous infusion on days 1–5
Radiation therapy:	6,600–7,600 cGy in 180–200 cGy fractions

Repeat cycle every 21–28 days for 3 cycles (167).

Concurrent Chemo-Radiation Therapy for Laryngeal Preservation

Cisplatin:	100 mg/m² IV on days 1, 22, and 43
Radiation therapy:	7,000 cGy in 200 cGy fractions

Administer cisplatin concurrently with radiation therapy (168).

Chemoradiotherapy for Nasopharyngeal Cancer

Cisplatin:	100 mg/m² IV on days 1, 22, and 43 during radiotherapy
Radiation therapy:	Total dose of 7,000 cGy in 180–200 cGy fractions

At the completion of chemoradiotherapy, chemotherapy is administered as follows:

Cisplatin:	80 mg/m² IV on day 1
5-Fluorouracil:	1,000 mg/m²/day IV continuous infusion on days 1–4

Repeat cycle every 28 days for a total of 3 cycles (169).

Carboplatin + 5-Fluorouracil

Carboplatin:	300–400 mg/m² IV on day 1
5-Fluorouracil:	600 mg/m² IV on day 1

Repeat cycle every 21 days (170).

VP

Vinorelbine:	25 mg/m² IV on days 1 and 8
Cisplatin:	80 mg/m² IV on day 1

Repeat cycle every 21 days (171).

Single-Agent Regimens

Docetaxel

Docetaxel: 100 mg/m^2 IV over 1 hour on day 1

Repeat cycle every 21 days (172).

Paclitaxel

Paclitaxel: 250 mg/m^2 IV over 24 hours on day 1

Repeat cycle every 21 days (173).

or

Paclitaxel: 137–175 mg/m^2 IV over 3 hours on day 1

Repeat cycle every 21 days (173).

Methotrexate

Methotrexate: 40 mg/m^2 IV or IM weekly

Repeat cycle every week (174).

Vinorelbine

Vinorelbine: 30 mg/m^2 IV weekly

Repeat cycle every week (175).

HEPATOCELLULAR CANCER

Single-Agent Regimens

Doxorubicin

Doxorubicin: 20–30 mg/m^2 IV weekly

Repeat cycle every week (176).

Cisplatin

Cisplatin: 80 mg/m^2 IV on day 1

Repeat cycle every week (177).

Capecitabine

Capecitabine: 1,000 mg/m^2 PO bid on days 1–14

Repeat cycle every 21 days (178). Dose may be reduced to 825–900 mg/m² PO bid on days 1–14. This dose reduction may decrease the risk of toxicity without compromising clinical efficacy.

KAPOSI'S SARCOMA

Combination Regimens

BV

Bleomycin: 10 U/m² IV on days 1 and 15

Vincristine: 1.4 mg/m² IV on days 1 and 15 (maximum, 2 mg)

Repeat cycle every 2 weeks (179).

ABV

Doxorubicin: 40 mg/m² IV on day 1

Bleomycin: 15 U/m² IV on days 1 and 15

Vinblastine: 6 mg/m² IV on day 1

Repeat cycle every 28 days (180).

Single-Agent Regimens

Liposomal Daunorubicin

DaunoXome: 40 mg/m² IV on day 1

Repeat cycle every 14 days (181).

Liposomal Doxorubicin

Doxil: 20 mg/m² IV on day 1

Repeat cycle every 21 days (182).

Paclitaxel

Paclitaxel: 135 mg/m² IV over 3 hours on day 1

Repeat cycle every 21 days (183).

or

Paclitaxel:

Repeat cycle every 2 weeks (184).

Interferon-α

Interferon α-2a:	36 million IU/m² SC or IM, daily for 8–12 weeks (185)
Interferon α-2b:	30 million IU/m² SC or IM, 3 times weekly (186)

LEUKEMIA

Acute Lymphocytic Leukemia

Induction Therapy

Linker Regimen (187, 188)

Daunorubicin:	50 mg/m² IV every 24 hours on days 1–3
Vincristine:	2 mg IV on days 1, 8, 15, and 22
Prednisone:	60 mg/m² PO divided into 3 doses on days 1–28
L-Asparaginase:	6,000 U/m² IM on days 17–28
If bone marrow on day 14 is positive for residual leukemia,	
Daunorubicin:	50 mg/m² IV on day 15
If bone marrow on day 28 is positive for residual leukemia,	
Daunorubicin:	50 mg/m² IV on days 29 and 30
Vincristine:	2 mg IV on days 29 and 36
Prednisone:	60 mg/m² PO on days 29–42
L-Asparaginase:	6,000 U/m² IM on days 29–35

Consolidation Therapy

Linker Regimen (187, 188)

Treatment A (cycles 1, 3, 5, and 7)	
Daunorubicin:	50 mg/m² IV on days 1 and 2
Vincristine:	2 mg IV on days 1 and 8
Prednisone:	60 mg/m² PO on days 1–14
L-Asparaginase:	12,000 U/m² on days 2, 4, 7, 9, 11, and 14
Treatment B (cycles 2, 4, 6, and 8)	
Teniposide:	165 mg/m² IV on days 1, 4, 8, and 11

Cytarabine:	300 mg/m² IV on days 1, 4, 8, and 11
Treatment C (cycle 9)	
Methotrexate:	690 mg/m² IV over 42 hours
Leucovorin:	15 mg/m² IV every 6 hours for 12 doses beginning at 42 hours

Maintenance Therapy

Linker Regimen (187, 188)

Methotrexate:	20 mg/m² PO weekly
6-Mercaptopurine:	75 mg/m² PO daily

Continue for a total of 30 months of complete response.

CNS Prophylaxis

Cranial irradiation:	1,800 rad in 10 fractions over 12–14 days
Methotrexate:	12 mg IT weekly for 6 weeks

Begin within 1 week of complete response.

In patients with documented CNS involvement at time of diagnosis, intrathecal chemotherapy should begin during induction chemotherapy.

Methotrexate:	12 mg IT weekly for 10 doses
Cranial irradiation:	2,800 rad

Induction Therapy

Larson Regimen (189)

Induction (weeks 1–4)	
Cyclophosphamide:	1,200 mg/m² IV on day 1
Daunorubicin:	45 mg/m² IV on days 1–3
Vincristine:	2 mg IV on days 1, 8, 15, and 22
Prednisone:	60 mg/m²/day PO on days 1–21
L-Asparaginase:	6,000 IU/m² SC on days 15, 18, 22, and 25
Early Intensification (weeks 5–12)	
Methotrexate:	15 mg IT on day 1
Cyclophosphamide:	1,000 mg/m² IV on day 1

6-Mercaptopurine:	60 mg/m²/day PO on days 1–4 and 8–11
Cytarabine:	75 mg/m² IV on days 1–14
Vincristine:	2 mg IV on days 15 and 22
L-Asparaginase:	6,000 IU/m² SC on days 15, 18, 22, and 25

Repeat the early intensification cycle once.

CNS Prophylaxis and Interim Maintenance (weeks 13–25)

Cranial irradiation:	2,400 cGy on days 1–12
Methotrexate:	15 mg IT on days 1, 8, 15, 22, and 29
6-Mercaptopurine:	60 mg/m²/day PO on days 1–70
Methotrexate:	20 mg/m² PO on days 36, 43, 50, 57, and 64

Late Intensification (weeks 26–33)

Doxorubicin:	30 mg/m² IV on days 1, 8, and 15
Vincristine:	2 mg IV on days 1, 8, and 15
Dexamethasone:	10 mg/m²/day PO on days 1–14
Cyclophosphamide:	1,000 mg/m² IV on day 29
6-Thioguanine:	60 mg/m²/day PO on days 29–42
Cytarabine:	75 mg/m² on days 29, 32, 36–39

Prolonged Maintenance (continue until 24 months after diagnosis)

Vincristine:	2 mg IV on day 1
Prednisone:	60 mg/m²/day PO on days 1–5
Methotrexate:	20 mg/m² PO on days 1, 8, 15, and 22
6-Mercaptopurine:	80 mg/m²/day PO on days 1–28

Repeat maintenance cycle every 28 days.

Hyper-CVAD Regimen

Cyclophosphamide:	300 mg/m² IV over 3 hours every 12 hours for 6 doses on days 1–3
Mesna:	600 mg/m² IV over 24 hours on days 1–3 ending 6 hours after the last dose of cyclophosphamide
Vincristine:	2 mg IV on days 4 and 11
Doxorubicin:	50 mg/m² IV on day 4

Dexamethasone:	40 mg PO or IV on days 1–4 and 11–14

Alternate cycles every 21 days with the following:

Methotrexate:	200 mg/m² IV over 2 hours, followed by 800 mg/m² IV over 24 hours on day 1
Leucovorin:	15 mg IV every 6 hours for 8 doses, starting 24 hours after the completion of methotrexate infusion
Cytarabine:	3,000 mg/m² IV over 2 hours every 12 hours for 4 doses on days 2–3
Methylprednisolone:	50 mg IV bid on days 1–3

Alternate 4 cycles of hyper-CVAD with 4 cycles of high-dose methotrexate and cytarabine therapy (190).

CNS Prophylaxis

Methorexate:	12 mg IT on day 2
Cytarabine:	100 mg IT on day 8

Repeat with each cycle of chemotherapy, depending on the risk of CNS disease.

Supportive Care

Ciprofloxacin:	500 mg PO bid
Fluconazole:	200 mg/day PO
Acyclovir:	200 mg PO bid
G-CSF:	10 μg/kg/day starting 24 hours after the end of chemotherapy (i.e., on day 5 of hyperCVAD therapy and on day 4 of high-dose methotrexate and cytarabine therapy)

Single-Agent Regimens

Clofarabine

Clofarabine:	52 mg/m² IV for 5 days

Repeat cycle every 2–6 weeks (191).

Acute Myelogenous Leukemia

Induction Regimens

Ara-C + Daunorubicin (7 + 3) (192)

Cytarabine:	100 mg/m²/day IV continuous infusion on days 1–7
Daunorubicin:	45 mg/m² IV on days 1–3

Ara-C + Idarubicin (193)

Cytarabine:	100 mg/m²/day IV continuous infusion on days 1–7
Idarubicin:	12 mg/m² IV on days 1–3

Ara-C + Doxorubicin (194)

Cytarabine:	100 mg/m²/day IV continuous infusion on days 1–7
Doxorubicin:	30 mg/m² IV on days 1–3

AIDA (acute promyelocytic leukemia only) (195)

ATRA:	45 mg/m² PO daily
Idarubicin:	12 mg/m² IV on days 2, 4, 6, and 8

Consolidation Regimens

Ara-C + Daunorubicin (5 + 2) (196)

Cytarabine:	100 mg/m²/day IV continuous infusion on days 1–5
Daunorubicin:	45 mg/m² IV on days 1 and 2

Ara-C + Idarubicin (196)

Cytarabine:	100 mg/m² IV continuous infusion on days 1–5
Idarubicin:	13 mg/m² IV on days 1 and 2

Repeat cycle every 21–28 days.

Single-Agent Regimens

Cladribine (197)

Cladribine:	0.1 mg/kg/day IV continuous infusion on days 1–7

High-Dose Cytarabine

Cytarabine:	3,000 mg/m^2 IV over 3 hours, every 12 hours on days 1, 3, and 5

Repeat cycle every 28 days (198).

ATRA (acute promyelocytic leukemia only) (199)

ATRA:	45 mg/m^2 PO daily in 1–2 divided doses

Gemtuzumab

Gemtuzumab:	9 mg/m^2 IV as a 2-hour infusion

Repeat with a second dose 14 days after administration of the first dose (200). Premedicate with diphenhydramine 50 mg PO and acetaminophen 650–1,000 mg PO, 1 hour before drug infusion. Once the infusion is completed, give 2 additional doses of acetaminophen 650–1,000 mg PO every 4 hours.

Chronic Lymphocytic Leukemia

Combination Regimens

CVP

Cyclophosphamide:	400 mg/m^2 PO on days 1–5 (or 800 mg/m^2 IV on day 1)
Vincristine:	1.4 mg/m^2 IV on day 1 (maximum dose, 2 mg)
Prednisone:	100 mg/m^2 PO on days 1–5

Repeat cycle every 21 days (201).

CF

Cyclophosphamide:	1,000 mg/m^2 IV on day 1
Fludarabine:	20 mg/m^2 IV on days 1–5
Bactrim DS:	1 tablet PO bid

Repeat cycle every 21–28 days (202).

FP

Fludarabine: 30 mg/m² IV on days 1–5

Prednisone: 30 mg/m² IV on days 1–5

Repeat cycle every 28 days (203).

CP

Chlorambucil: 30 mg/m² PO on day 1

Prednisone: 80 mg PO on days 1–5

Repeat cycle every 28 days (201).

FR

Fludarabine: 30 mg/m² IV on days 1–5

Rituximab: 375 mg/m² IV on days 1, 3, and 5

Repeat cycle every 28 days (204).

FCR

Fludarabine: 25 mg/m² IV on days 1–3

Cyclophosphamide: 250 mg/m² IV on days 1-3

Rituximab: 375–500 mg/m² IV on day 1

Repeat cycle every 28 days (205).

Single-Agent Regimens

Alemtuzumab

Alemtuzumab: 30 mg/day IV, 3 times per week

Repeat weekly for up to a maximum of 23 weeks (206). Premedicate with diphenhydramine 50 mg PO and acetaminophen 625 mg PO 30 minutes before drug infusion. Patients should be placed on Bactrim DS PO bid and famciclovir 250 mg PO bid from day 8 through 2 months following completion of therapy.

Chlorambucil

Chlorambucil: 6–14 mg/day PO as induction therapy and then 0.7 mg/kg PO for 2–4 days

Repeat cycle every 21 days (207).

Cladribine

Cladribine: 0.09 mg/kg/day IV continuous infusion on days 1–7

Repeat cycle every 28–35 days (208).

Fludarabine

Fludarabine: 20–30 mg/m^2 IV on days 1–5

Repeat cycle every 28 days (209).

Prednisone

Prednisone: 20–30 mg/m^2/day PO for 1–3 weeks (210).

Chronic Myelogenous Leukemia

Combination Regimens

Interferon + Cytarabine

Interferon α-2b: 5×10^6 IU/m^2 SC daily

Cytabarabine: 20 mg/m^2 SC daily for 10 days

Repeat cytarabine on a monthly basis (211). The dose of interferon should be reduced by 50% when the neutrophil count drops below 1,500/mm^3, the platelet count drops below 100,000/m^3, or both. Interferon and cytarabine should both be discontinued when the neutrophil count drops below 1,000/mm^3, platelet count drops below 50,000/mm^3, or both.

Single-Agent Regimens

Imatinib

Imatinib: 400 mg/day PO (chronic phase) 600 mg/day PO (accelerated phase blast crisis) (212)

Busulfan

Busulfan: 1.8 mg/m^2/day PO (213)

Hydroxyurea

Hydroxyurea: 1–5 gm/day PO (214)

Interferon α-2a

Interferon α-2a: 9 million units/day SC (215)

Hairy Cell Leukemia

Cladribine

Cladribine: 0.09 mg/kg/day IV continuous infusion on days 1–7

Administer one cycle (216).

Pentostatin

Pentostatin: 4 mg/m² IV on day 1

Repeat cycle every 14 days for 6 cycles (217).

Interferon α-2a

Interferon α-2a: 3 million units SC or IM, 3 times per week

Continue treatment for up to 1 to 1.5 years (218).

LUNG CANCER

Non-Small Cell Lung Cancer

Adjuvant Therapy

Combination Regimens

Paclitaxel + Carboplatin

Paclitaxel: 175 mg/m² IV over 3 hours on day 1

Carboplatin: AUC of 6, IV on day 1

Repeat cycle every 21 days for 4 cycles (219).

Vinorelbine + Cisplatin

Vinorelbine: 25 mg/m² IV weekly for 16 weeks

Cisplatin: 50 mg/m² IV on days 1 and 8

Repeat cisplatin every 28 days for 4 cycles (220).

Metastatic Disease

Combination Regimens

Carboplatin + Paclitaxel

Carboplatin: AUC of 6, IV on day 1

Paclitaxel: 175 mg/m² IV over 3 hours on day 1

Repeat cycle every 21 days (221).

Cisplatin + Paclitaxel

Cisplatin: 80 mg/m² IV on day 1

Paclitaxel: 175 mg/m² IV over 3 hours on day 1

Repeat cycle every 21 days (222).

Important to administer paclitaxel first followed by cisplatin.

Docetaxel + Carboplatin

Docetaxel: 75 mg/m² IV on day 1

Carboplatin: AUC of 6, IV on day 1

Repeat cycle every 21 days (223).

Docetaxel + Cisplatin

Docetaxel: 75 mg/m² IV on day 1

Cisplatin: 75 mg/m² IV on day 1

Repeat cycle every 21 days (224).

Docetaxel + Gemcitabine

Docetaxel: 100 mg/m² IV on day 8

Gemcitabine: 1,100 mg/m² IV on days 1 and 8

Repeat cycle every 21 days (225). G-CSF support is required from day 9 to day 15.

Gemcitabine + Cisplatin

Gemcitabine: 1,250 mg/m² IV on days 1 and 8

Cisplatin: 100 mg/m² IV on day 1

Repeat cycle every 21 days (226).

Gemcitabine + Carboplatin

Gemcitabine: 1,000 mg/m² IV on days 1 and 8

Carboplatin: AUC of 5, IV on day 1

Repeat cycle every 21 days (227).

Gemcitabine + Vinorelbine

Gemcitabine: 1,200 mg/m² IV on days 1 and 8

Vinorelbine: 30 mg/m² IV on days 1 and 8

Repeat cycle every 21 days (228).

Vinorelbine + Cisplatin

Vinorelbine: 30 mg/m² IV on days 1, 8, and 15

Cisplatin: 120 mg/m² IV on day 1

Repeat cycle every 28 days (229).

Vinorelbine + Carboplatin

Vinorelbine: 25 mg/m² IV on days 1 and 8

Carboplatin: AUC of 6, IV on day 1

Repeat cycle every 28 days (230).

EP

Etoposide (VP-16): 120 mg/m² IV on days 1–3

Cisplatin: 60 mg/m² IV on day 1

Repeat cycle every 21–28 days (231).

EP and Docetaxel

Cisplatin: 50 mg/m² IV on days 1, 8, 29, and 36

Etoposide: 50 mg/m² IV on days 1–5 and 29–33

Administer concurrent thoracic radiotherapy, followed 4–6 weeks after the completion of combined modality therapy by

Docetaxel: 75 mg/m² IV on day 1

Repeat cycle every 21 days for 3 cycles (232). Dose of docetaxel can be escalated to 100 mg/m² IV on subsequent cycles in the absence of toxicity.

Single-Agent Regimens

Paclitaxel

Paclitaxel: 225 mg/m² IV over 3 hours on day 1

Repeat cycle every 21 days (233).
or

Paclitaxel: 80–100 mg/m² IV weekly for 3 weeks

Repeat cycle every 28 days after 1-week rest (234).

Docetaxel

Docetaxel: 75 mg/m² IV on day 1

Repeat cycle every 21 days (235).
or

Docetaxel: 36 mg/m² IV weekly for 6 weeks

Repeat cycle every 8 weeks after 2-week rest (236). Premedicate with dexamethasone 8 mg PO at 12 hours and immediately before docetaxel infusion and 12 hours after each dose.

Pemetrexed

Pemetrexed: 500 mg/m² IV on day 1

Folic acid at 350–1,000 μg PO q day beginning one week prior to therapy and vitamin B12 at 1,000 μg IM beginning 1–2 weeks prior to first dose of therapy and repeated every 3 cycles. Repeat cycle every 21 days (237).

Gemcitabine

Gemcitabine: 1,000 mg/m² IV on days 1, 8, and 15

Repeat cycle every 28 days (238).

Topotecan

Topotecan: 1.5 mg/m² IV on days 1–5

Repeat cycle every 21 days (239).

Vinorelbine

Vinorelbine: 25 mg/m² IV every 7 days

Repeat every 7 days (240).

Gefitinib

Gefitinib: 250 mg/day PO

Continue treatment until disease progression (241).

Erlotinib

Erlotinib: 150 mg PO

Continue treatment until disease progression (242).

Small Cell Lung Cancer

Combination Regimens

EP

Etoposide: 80 mg/m² IV on days 1–3

Cisplatin: 80 mg/m² IV on day 1

Repeat cycle every 21 days (243).

EC

Etoposide: 100 mg/m² IV on days 1–3

Carboplatin: AUC of 6, IV on day 1

Repeat cycle every 28 days (244).

Irinotecan + Cisplatin

Irinotecan: 60 mg/m² IV on days 1, 8, and 15

Cisplatin: 60 mg/m² IV on day 1

Repeat cycle every 28 days (245).

Carboplatin + Paclitaxel + Etoposide

Carboplatin: AUC of 6, IV on day 1

Paclitaxel: 200 mg/m² IV over 1 hour on day 1

Etoposide: 50 mg alternating with 100 mg PO on days 1–10

Repeat cycle every 21 days (246).

CAV

Cyclophosphamide: 1,000 mg/m² IV on day 1

Doxorubicin: 40 mg/m² IV on day 1

Vincristine: 1 mg/m² IV on day 1 (maximum, 2 mg)

Repeat cycle every 21 days (247).

CAE

Cyclophosphamide: 1,000 mg/m² IV on day 1

Doxorubicin: 45 mg/m² IV on day 1

Etoposide: 50 mg/m² IV on days 1–5

Repeat cycle every 21 days (248).

Single-Agent Regimens

Etoposide

Etoposide: 160 mg/m² PO on days 1–5

Repeat cycle every 28 days (249).
or

Etoposide: 50 mg/m² PO bid on days 1–21

Repeat cycle as tolerated (250).

Paclitaxel

Paclitaxel: 80–100 mg/m² IV weekly for 3 weeks

Repeat cycle every 28 days (251).

Topotecan

Topotecan: 1.5 mg/m² IV on days 1–5

Repeat cycle every 21 days (252).

LYMPHOMA

Hodgkin's Disease

ABVD

Doxorubicin: 25 mg/m² IV on days 1 and 15

Bleomycin: 10 U/m² IV on days 1 and 15

Vinblastine: 6 mg/m² IV on days 1 and 15

Dacarbazine: 375 mg/m² IV on days 1 and 15

Repeat cycle every 28 days (253).

MOPP

Nitrogen mustard: 6 mg/m² IV on days 1 and 8

Vincristine: 1.4 mg/m² IV on days 1 and 8

Procarbazine: 100 mg/m² PO on days 1–14

Prednisone: 40 mg/m² PO on days 1–14

Repeat cycle every 28 days (254).

MOPP/ABVD Hybrid

Nitrogen mustard:	6 mg/m² IV on days 1 and 8
Vincristine:	1.4 mg/m² IV on day 1 (maximum dose, 2 mg)
Procarbazine:	100 mg/m² PO on days 1–14
Prednisone:	40 mg/m² PO on days 1–14
Doxorubicin:	35 mg/m² IV on day 8
Bleomycin:	10 U/m² IV on day 8
Hydrocortisone:	100 mg IV given before bleomycin
Vinblastine:	6 mg/m² IV on day 8

Repeat cycle every 28 days (255).

MOPP alternating with ABVD

See MOPP and ABVD regimens outlined above.

Stanford V

Nitrogen mustard:	6 mg/m² IV on day 1
Doxorubicin:	25 mg/m² IV on days 1 and 15
Vinblastine:	6 mg/m² IV on days 1 and 15
Vincristine:	1.4 mg/m² IV on days 8 and 22
Bleomycin:	5 U/m² IV on days 8 and 22
Etoposide:	60 mg/m² IV on days 15 and 16
Prednisone:	40 mg PO every other day

Repeat cycle every 28 days (256). In patients > 50 years of age, vinblastine dose reduced to 4 mg/m² and vincristine dose reduced to 1 mg/m² on weeks 9 and 12. Dose of prednisone tapered starting on week 10. Prophylactic Bactrim DS PO bid and acyclovir 200 mg PO tid.

EVA

Etoposide:	200 mg/m² IV on days 1–5
Vincristine:	2 mg/m² IV on day 1
Doxorubicin:	50 mg/m² IV on day 2

Repeat cycle every 28 days (256a).

EVAP

Etoposide:	120 mg/m² IV on days 1, 8, and 15
Vinblastine:	4 mg/m² IV on days 1, 8, and 15
Cytarabine:	30 mg/m² IV on days 1, 8, and 15
Cisplatin:	40 mg/m² IV on days 1, 8, and 15

Repeat cycle every 28 days (257).

Mini-BEAM

BCNU:	60 mg/m² IV on day 1
Etoposide:	75 mg/m² IV on days 2–5
Ara-C:	100 mg/m² IV every 12 hours on days 2–5
Melphalan:	30 mg/m² IV on day 6

Repeat cycle every 4–6 weeks (258).

BEACOPP

Bleomycin:	10 mg/m² IV on day 8
Etoposide:	100 mg/m² IV on days 1–3
Doxorubicin:	25 mg/m² IV on day 1
Cyclophosphamide:	650 mg/m² IV on day 1
Vincristine:	1.4 mg/m² IV on day 8 (maximum, 2 mg)
Procarbazine:	100 mg/m² PO on days 1–7
Prednisone:	40 mg/m² PO on days 1–14

Repeat cycle every 21 days (259).

BEACOPP Escalated

Bleomycin:	10 mg/m² IV on day 8
Etoposide:	200 mg/m² IV on days 1–3
Doxorubicin:	35 mg/m² IV on day 1
Cyclophosphamide:	1,200 mg/m² IV on day 1
Vincristine:	1.4 mg/m² IV on day 8 (maximum dose, 2 mg)
Procarbazine:	100 mg/m² PO on days 1–7

Prednisone: 40 mg/m² PO on days 1–14

Repeat cycle every 21 days (260). G-CSF, at dose of 5 μg/kg/day SC, starting on day 8 and continue until neutrophil recovery.

Gemcitabine

Gemcitabine: 1,250 mg/m² IV on days 1, 8, and 15

Repeat cycle every 28 days (261).

NON-HODGKIN'S LYMPHOMA

Low-Grade

Combination Regimens

CVP

Cyclophosphamide: 400 mg/m² PO on days 1–5 (or 800 mg/m² IV on day 1)

Vincristine: 1.4 mg/m² IV on day 1 (maximum, 2 mg)

Prednisone: 100 mg/m² PO on days 1–5

Repeat cycle every 21 days (262).

CHOP

Cyclophosphamide: 750 mg/m² IV on day 1

Doxorubicin: 50 mg/m² IV on day 1

Vincristine: 1.4 mg/m² IV on day 1 (maximum, 2 mg)

Prednisone: 100 mg/m² PO on days 1–5

Repeat cycle every 21 days (263).

CNOP

Cyclophosphamide: 750 mg/m² IV on day 1

Mitoxantrone: 10 mg/m² IV on day 1

Vincristine: 1.4 mg/m² IV on day 1 (maximum, 2 mg)

Prednisone: 50 mg/m² PO on days 1–5

Repeat cycle every 21 days (264).

FND

Fludarabine: 25 mg/m² IV on days 1–3

Mitoxantrone: 10 mg/m² IV on day 1

Dexamethasone: 20 mg PO on days 1–5

Bactrim DS: 1 tablet PO bid, 3 times per week

Repeat cycle every 21 days (265).

FC

Fludarabine: 20 mg/m² IV on days 1–5

Cyclophosphamide: 1,000 mg/m² IV on day 1

Bactrim DS: 1 tablet PO bid

Repeat cycle every 21–28 days (266).

Bortezomib (mantle cell lymphoma)

Bortezomib: 1.5 mg/m² IV on days 1, 4, 8, and 11

Repeat cycle every 21 days (267).

Intermediate-Grade

CHOP

Cyclophosphamide: 750 mg/m² IV on day 1

Doxorubicin: 50 mg/m² IV on day 1

Vincristine: 1.4 mg/m² IV on day 1 (maximum, 2 mg)

Prednisone: 100 mg PO on days 1–5

Repeat cycle every 21 days (263).

CHOP + Rituximab (GELA Study)

Cyclophosphamide: 750 mg/m² IV on day 1

Doxorubicin: 50 mg/m² IV on day 1

Vincristine: 1.4 mg/m² IV on day 1 (maximum, 2 mg)

Prednisone: 40 mg/m² PO on days 1–5

Rituximab: 375 mg/m² IV on day 1

Repeat cycle every 21 days (268). Rituximab is to be administered first followed by cyclophosphamide, doxorubicin, and vincristine.
or

CHOP + Rituximab (Nebraska regimen)

Cyclophosphamide:	750 mg/m² IV on day 3
Doxorubicin:	50 mg/m² IV on day 3
Vincristine:	1.4 mg/m² IV on day 3 (maximum, 2 mg)
Prednisone:	100 mg PO on days 3–7
Rituximab:	375 mg/m² IV on day 1

Repeat cycle every 21 days (269).

CNOP

Cyclophosphamide:	750 mg/m² IV on day 1
Mitoxantrone:	10 mg/m² IV on day 1
Vincristine:	1.4 mg/m² IV on day 1 (maximum, 2 mg)
Prednisone:	100 mg PO on days 1–5

Repeat cycle every 21 days (270).

EPOCH

Etoposide:	50 mg/m²/day IV continuous infusion on days 1–4
Prednisone:	60 mg/m² PO on days 1–5
Vincristine:	0.4 mg/m²/day IV continuous infusion on days 1–4
Cyclophosphamide:	750 mg/m² IV on day 5, begin after infusion
Doxorubicin:	10 mg/m²/day IV continuous infusion on days 1–4
Bactrim DS:	1 tablet PO bid, 3 times per week

Repeat cycle every 21 days (271).

EPOCH + Rituximab

Etoposide:	50 mg/m²/day IV continuous infusion on days 1–4
Prednisone:	60 mg/m² PO bid on days 1–5
Vincristine:	0.4 mg/m²/day IV continuous infusion on days 1–4
Cyclophosphamide:	750 mg/m² IV on day 5, begin after infusion

Doxorubicin:	10 mg/m²/day IV continuous infusion on days 1–4
Rituximab:	375 mg/m² IV on day 1

Repeat cycle every 21 days (272). Rituximab is to be administered first followed by infusions of etoposide, doxorubicin, and vincristine. Prophylaxis with Bactrim DS 1 tab PO bid, 3 times per week to reduce the risk of *Pneumocystis carinii* infection.

MACOP-B

Methotrexate:	400 mg/m² IV on weeks 2, 6, and 10
Leucovorin:	15 mg/m² PO every 6 hours for 6 doses, beginning 24 hours after methotrexate
Doxorubicin:	50 mg/m² IV on weeks 1, 3, 5, 7, 9, and 11
Cyclophosphamide:	350 mg/m² IV on weeks 1, 3, 5, 7, 9, and 11
Vincristine:	1.4 mg/m² IV on weeks 2, 4, 6, 8, 10, and 12
Prednisone:	75 mg/day PO for 12 weeks with taper over the last 2 weeks
Bleomycin:	10 U/m² IV on weeks 4, 8, and 12
Bactrim DS:	1 tablet PO bid
Ketoconazole:	200 mg/day PO

Administer one cycle (273).

m-BACOD

Methotrexate:	200 mg/m² IV on days 8 and 15
Leucovorin:	10 mg/m² PO every 6 hours for 8 doses, beginning 24 hours after methotrexate
Bleomycin:	4 U/m² IV on day 1
Doxorubicin:	45 mg/m² IV on day 1
Cyclophosphamide:	600 mg/m² IV on day 1
Vincristine:	1 mg/m² IV on day 1 (maximum, 2 mg)
Dexamethasone:	6 mg/m² PO on days 1–5

Repeat cycle every 21 days (274).

ProMACE/CytaBOM

Prednisone:	60 mg/m² PO on days 1–14

Doxorubicin:	25 mg/m² IV on day 1
Cyclophosphamide:	650 mg/m² IV on day 1
Etoposide:	120 mg/m² IV on day 1
Cytarabine:	300 mg/m² IV on day 8
Bleomycin:	5 U/m² IV on day 8
Vincristine:	1.4 mg/m² IV on day 8
Methotrexate:	120 mg/m² IV on day 8
Leucovorin rescue:	25 mg/m² PO every 6 hours for 6 doses, beginning 24 hours after methotrexate
Bactrim DS:	1 tablet PO bid on days 1–21

Repeat cycle every 21 days (275).

ESHAP (salvage regimen)

Etoposide:	40 mg/m² IV on days 1–4
Methylprednisolone:	500 mg IV on days 1–4
Cisplatin:	25 mg/m²/day IV continuous infusion on days 1–4
Cytarabine:	2,000 mg/m² IV on day 5 after completion of cisplatin and etoposide

Repeat cycle every 21 days (276).

DHAP (salvage regimen)

Cisplatin:	100 mg/m² IV on day 1
Cytarabine:	2,000 mg/m² IV over 2 hours every 12 hours for 2 doses on day 1
Dexamethasone:	40 mg PO on day 14

Repeat cycle every 3–4 weeks (277).

ICE (salvage regimen)

Ifosfamide:	5,000 mg/m² IV continuous infusion for 24 hours on day 2
Etoposide:	100 mg/m² IV on days 1–3
Carboplatin:	AUC of 5, IV on day 2
Mesna:	5,000 mg/m² IV in combination with ifosfamide dose

Repeat cycle every 14 days (278). G-CSF is administered at 5 μg/kg on days 5–12.

MINE (salvage regimen)

Mesna:	1,330 mg/m² IV administered at same time as ifosfamide on days 1–3, then 500 mg IV 4 hours after ifosfamide on days 1–3
Ifosfamide:	1,330 mg/m² IV on days 1–3
Mitoxantrone:	8 mg/m² IV on day 1
Etoposide:	65 mg/m² IV on days 1–3

Repeat cycle every 21 days (279).

High-Grade

Magrath Protocol (Burkitt's lymphoma)

Cyclophosphamide:	1,200 mg/m² IV on day 1
Doxorubicin:	40 mg/m² IV on day 1
Vincristine:	1.4 mg/m² IV on day 1 (maximum, 2 mg)
Prednisone:	40 mg/m² PO on days 1–5
Methotrexate:	300 mg/m² IV on day 10, for 1 hour, then 60 mg/m² IV on days 10 and 11, for 41 hours
Leucovorin rescue:	15 mg/m² IV every 6 hours for 8 doses, starting 24 hours after methotrexate on day 12
Intrathecal ara-C:	30 mg/m² IT on day 7, cycle 1 only 45 mg/m² IT on day 7, all subsequent cycles
Intrathecal methotrexate:	12.5 mg IT on day 10, all cycles

Repeat cycle every 28 days (280).
or

Regimen A (CODOX-M) (281)

Cyclophosphamide:	800 mg/m² IV on day 1 and 200 mg/m² IV on days 2–5
Doxorubicin:	40 mg/m² IV on day 1
Vincristine:	1.5 mg/m² IV on days 1 and 8 in cycle 1 and on days 1, 8, and 15 in cycle 3

Methotrexate:	1,200 mg/m² IV over 1 hour, followed by 240 mg/m²/hour for the next 23 hours on day 10
Leucovorin:	192 mg/m² IV starting at hour 36 after the start of the infusion and 12 mg/m² IV every 6 hours thereafter until serum MTX levels < 50 nM

CNS prophylaxis

Cytarabine:	70 mg IT on days 1 and 3
Methotrexate:	12 mg IT on day 15

Regimen B (IVAC)

Ifosfamide:	1,500 mg/m² IV on days 1–5
Etoposide:	60 mg/m² IV on days 1–5
Cytarabine:	2 g/m² IV every 12 hours on days 1 and 2 for a total of 4 doses
Methotrexate:	12 mg IT on day 5

Stanford Regimen (small non-cleaved cell and Burkitt's lymphoma)

Cyclophosphamide:	1,200 mg/m² IV on day 1
Doxorubicin:	40 mg/m² IV on day 1
Vincristine:	1.4 mg/m² IV on day 1 (maximum, 2 mg)
Prednisone:	40 mg/m² PO on days 1–5
Methotrexate:	3 g/m² IV over 6 hours on day 10
Leucovorin rescue:	25 mg/m² IV or PO every 6 hours for 12 doses, beginning 24 hours after methotrexate
Intrathecal methotrexate:	12 mg IT on days 1 and 10

Repeat cycle every 21 days (282).

PRIMARY CNS LYMPHOMA

Methotrexate:	3.5 gm/m² IV over 2 hours every other week for 5 doses
Intrathecal Methotrexate:	12 mg IT weekly every other week after IV MTX

Leucovorin:	10 mg IV every 6 hours for 12 doses, starting 24 hours after IV MTX 10 mg IV every 12 hours for 8 doses, starting 24 hours after IT MTX
Vincristine:	1.4 mg/m^2 IV every other week along with IV MTX
Procarbazine:	100 mg/m^2/day PO for 7 days on 1st, 3rd, and 5th cycle of IV MTX

Once chemotherapy is completed, whole brain radiation therapy to a total dose of 45 cGy (283).

Single-Agent Regimens

Rituximab

Rituximab:	375 mg/m^2 IV on days 1, 8, 15, and 22

May repeat one additional cycle (284).

Ibritumomab Tiuxetan Regimen

Rituximab:	250 mg/m^2 IV on days 1 and 8
^{111}In-Ibritumomab tiuxetan:	5 mCi of ^{111}In, 1.6 mg of ibritumomab tiuxetan IV on day 1
^{90}Y-Ibritumomab tiuxetan:	0.4 mCi/kg IV over 10 min on day 8 after the day 8 rituximab dose

The dose of ^{90}Y-ibritumomab tiuxetan is capped at 32 mCi (285).

Fludarabine

Fludarabine:	25 mg/m^2 IV on days 1–5

Repeat cycle every 28 days (286).

Cladribine

Cladribine:	0.5–0.7 mg/kg SC on days 1–5 or 0.1 mg/kg IV on days 1–7

Repeat cycle every 28 days (287).

MALIGNANT MELANOMA

Adjuvant Therapy

Interferon α-2b

Interferon α-2b: 20×10^6 IU/m² IV, 5 times weekly for 4 weeks, then 10×10^6 IU/m² SC, 3 times weekly for 48 weeks

Treat for a total of one year (288).

Metastatic Disease

Combination Regimens

DTIC + BCNU + Cisplatin

Dacarbazine: 220 mg/m² IV on days 1–3

Carmustine: 150 mg/m² IV on day 1

Cisplatin: 25 mg/m² IV on days 1–3

Repeat cycle with dacarbazine and cisplatin every 21 days and carmustine every 42 days (289).

DTIC + Cisplatin + BCNU + Tamoxifen (Dartmouth regimen)

Dacarbazine: 220 mg/m² IV on days 1–3 and 22–24

Cisplatin: 25 mg/m² IV on days 1–3 and 22–24

Carmustine: 150 mg/m² IV on day 1

Tamoxifen: 10 mg PO bid starting on day 4

Repeat cycle every 6 weeks (290).

CVD

Cisplatin: 20 mg/m² IV on days 1–5

Vinblastine: 1.6 mg/m² IV on days 1–5

Dacarbazine: 800 mg/m² IV on day 1

Repeat cycle every 21–28 days (291).

IFN + DTIC

Interferon α-2b: 15×10^6 IU/m² IV on days 1–5, 8–12, and 15–19 as induction therapy

Interferon α-2b:	10×10^6 IU/m² SC 3 times weekly after induction therapy
Dacarbazine:	200 mg/m² IV on days 22–26

Repeat cycle every 28 days (292).

Cisplatin + Vinblastine + DTIC + IL-2 + IFN

Cisplatin:	20 mg/m² IV on days 1–4 and 22–25
Vinblastine:	1.5 mg/m² IV on days 1–4 and 22–25
Dacarbazine:	800 mg/m² IV on days 1 and 22
Interleukin-2:	9 million IU/m² IV as a 24-hour continuous infusion on days 5–8 and 17–20
Interferon α-2b:	5 million IU/m² SC on days 5–9, 17–21, and 26–30

Repeat cycle every 6 weeks (293).

Temozolomide + Thalidomide

Temozolomide:	75 mg/m²/day PO for 6 weeks
Thalidomide:	200–400 mg/m²/day PO for 6 weeks

Repeat cycle every 10 weeks (294).

Single-Agent Regimens

Dacarbazine

Dacarbazine:	250 mg/m² IV on days 1–5

Repeat cycle every 21 days (295).
or

Dacarbazine:	850 mg/m² IV on day 1

Repeat cycle every 3–6 weeks (296).

Interferon-α

Interferon α-2b:	20 million IU/m² IM, 3 times weekly for 12 weeks (297)

Aldesleukin

Aldesleukin (IL-2):	100,000 IU/kg IV on days 1–5 and 15–19

Repeat cycle every 28 days (298).

Temozolomide

Temozolomide: 150 mg/m² PO on days 1–5

Repeat cycle every 28 days (299). If well tolerated, can increase dose to 200 mg/m² PO on days 1–5.

MALIGNANT MESOTHELIOMA

Combination Regimens

Doxorubicin + Cisplatin

Doxorubicin: 60 mg/m² IV on day 1

Cisplatin: 60 mg/m² IV on day 1

Repeat cycle every 21–28 days (300).

CAP

Cyclophosphamide: 500 mg/m² IV on day 1

Doxorubicin: 50 mg/m² IV on day 1

Cisplatin: 80 mg/m² IV on day 1

Repeat cycle every 21 days (301).

Gemcitabine + Cisplatin

Gemcitabine: 1,000 mg/m² IV on days 1, 8, and 15

Cisplatin: 100 mg/m² IV on day 1

Repeat cycle every 28 days (302).

Gemcitabine + Carboplatin

Gemcitabine: 1,000 mg/m² IV on days 1, 8, and 15

Carboplatin: AUC of 5, IV on day 1

Repeat cycle every 28 days (303).

Pemetrexed + Cisplatin

Pemetrexed: 500 mg/m² IV on day 1

Cisplatin: 75 mg/m² IV on day 1

Folic acid at 350–1,000 μg PO q day beginning one week prior to therapy and vitamin B12 at 1,000 μg IM to start 1–2 weeks prior to first dose of therapy and repeated every 3 cycles. Repeat cycle every 21 days (304).

MULTIPLE MYELOMA

Combination Regimens

MP

Melphalan: 8–10 mg/m^2 PO on days 1–4

Prednisone: 60 mg/m^2 on days 1–4

Repeat cycle every 42 days (305).

VAD

Vincristine: 0.4 mg/day IV continuous infusion on days 1–4

Doxorubicin: 9 mg/m^2/day IV continuous infusion on days 1–4

Dexamethasone: 40 mg PO on days 1–4, 9–12, and 17–20

Repeat cycle every 28 days (306).

Thalidomide + Dexamethasone

Thalidomide: 200 mg/day PO

Dexamethasone: 40 mg/day PO on days 1–4, 9–12, and 17–20 (odd cycles) 40 mg/day PO on days 1–4 (even cycles)

Repeat cycles every 28 days (307).

M2 Protocol

Vincristine: 0.03 mg/kg IV on day 1

Carmustine: 0.5 mg/kg IV on day 1

Melphalan: 0.25 mg/kg PO on days 1–4

Cyclophosphamide: 10 mg/kg IV on day 1

Prednisone: 1 mg/kg PO on days 1–7, taper after first week, discontinue on day 21

Repeat cycle every 35 days (308).

Single-Agent Regimens

Dexamethasone

Dexamethasone: 40 mg IV or PO on days 1–4, 9–12, and 17–20

Repeat cycle every 21 days (309).

Melphalan

Melphalan: 90–140 mg/m^2 IV on day 1

Repeat cycle every 28–42 days (310).

Thalidomide

Thalidomide: 200–800 mg PO daily

Continue treatment until disease progression or undue toxicity (311).

Bortezomib

Bortezomib: 1.3 mg/m^2 IV on days 1, 4, 8, and 11

Repeat cycle every 21 days (312).

If progressive disease after 2 cycles or stable disease after 4 cycles, may add Dexamethasone at 20 mg PO daily on the day of and the day after Bortezomib.

Interferon α-2b

Interferon α-2b: 2 million IU SC or IM, 3 times weekly

Use as maintenance therapy in patients with significant response to induction chemotherapy (313).

OVARIAN CANCER (Epithelial)

Combination Regimens

CC

Carboplatin: 300 mg/m^2 IV on day 1

Cyclophosphamide: 600 mg/m^2 IV on day 1

Repeat cycle every 28 days (314).

CP

Cisplatin: 100 mg/m^2 IV on day 1

Cyclophosphamide: 600 mg/m^2 IV on day 1

Repeat cycle every 28 days (315).

CT

Cisplatin: 75 mg/m² IV on day 2

Paclitaxel: 135 mg/m² IV over 24 hours on day 1

Repeat cycle every 21 days (316).

Carboplatin + Paclitaxel

Carboplatin: AUC of 6–7.5, IV on day 1

Paclitaxel: 175 mg/m² IV over 3 hours on day 1

Repeat cycle every 21 days (317).

Carboplatin + Docetaxel

Carboplatin: AUC of 6, IV on day 1

Docetaxel: 60 mg/m² IV on day 1

Repeat cycle every 21 days (318).

Gemcitabine + Liposomal Doxorubicin

Gemcitabine: 1,000 mg/m² IV on days 1 and 8

Doxil: 30 mg/m² IV on day 1

Repeat cycle every 21 days (319).

Gemcitabine + Cisplatin

Gemcitabine: 800–1,000 mg/m² IV on days 1 and 8

Cisplatin: 30 mg/m² IV on days 1 and 8

Repeat cycle every 21 days (320).

Single-Agent Regimens

Altretamine

Altretamine: 260 mg/m²/day PO in 4 divided doses after meals and at bedtime

Repeat cycle every 14–21 days (321).

Liposomal doxorubicin

Liposomal doxorubicin: 50 mg/m² IV over 1 hour on day 1

Repeat cycle every 28 days (322).

Paclitaxel

Paclitaxel: 135 mg/m² IV over 3 hours on day 1

Repeat cycle every 21 days (323).

Topotecan

Topotecan: 1.5 mg/m² IV on days 1–5

Repeat cycle every 21 days (324).

Gemcitabine

Gemcitabine: 800 mg/m² IV weekly for 3 weeks

Repeat cycle every 4 weeks (325).

Etoposide

Etoposide: 50 mg/m²/day PO on days 1–21

Repeat cycle every 28 days (326).

OVARIAN CANCER (Germ Cell)

Combination Regimens

BEP

Bleomycin: 30 U IV on days 2, 9, and 16

Etoposide: 100 mg/m² IV on days 1–5

Cisplatin: 20 mg/m² IV on days 1–5

Repeat cycle every 21 days (327).

PANCREAS CANCER

Locally Advanced Disease

5-Fluorouracil + Radiation Therapy (GITSG regimen)

5-Fluorouracil: 500 mg/m²/day IV on days 1–3 and 29–31, then weekly beginning on day 71

Radiation therapy: Total dose, 4,000 cGy

Chemotherapy and radiation therapy started on the same day and given concurrently (328).

Combination Regimens

5-Fluorouracil + Leucovorin

5-Fluorouracil: 425 mg/m² IV on days 1–5

Leucovorin: 20 mg/m² IV on days 1–5

Repeat cycle every 28 days (329).

Gemcitabine + Capecitabine

Gemcitabine: 1,000 mg/m² IV on days 1 and 8

Capecitabine: 650 mg/m² PO bid on days 1–14

Repeat cycle every 21 days (330).

Gemcitabine + Doctaxel + Capecitabine (GTX)

Gemcitabine: 750 mg/m² IV over 75 min on days 4 and 11

Docetaxel: 30 mg/m² IV on days 4 and 11

Capecitabine: 1,000–1,500 mg/m² PO bid on days 1–14

Repeat cycle every 2 weeks (331).

Gemcitabine + Cisplatin

Gemcitabine: 1,000 mg/m² IV on days 1, 8, and 15

Cisplatin: 50 mg/m² IV on days 1 and 15

Repeat cycle every 28 days (332).

Gemcitabine + Oxaliplatin

Gemcitabine: 1,000 mg/m² IV over 100 minutes at 10 mg/m²/min on day 1

Oxaliplatin: 100 mg/m² over 2 hours on day 2

Repeat cycle every 2 weeks (333).

Gemcitabine + Irinotecan

Gemcitabine: 1,000 mg/m² IV over 30 minutes on days 1 and 8

Irinotecan: 100 mg/m² IV over 90 minutes on days 1 and 8

Repeat cycle every 21 days (334).

FAM

5-Fluorouracil: 600 mg/m² IV on days 1, 8, 29, and 36

Doxorubicin: 30 mg/m² IV on days 1 and 29

Mitomycin-C: 10 mg/m² IV on day 1

Repeat cycle every 56 days (335).

Gemcitabine + Erlotinib

Gemcitabine: 1,000 mg/m² IV weekly for 7 weeks, then 1 week rest, subsequent cycles 1,000 mg/m² IV weekly for 3 weeks with 1 week rest

Erlotinib: 100 mg PO daily

Repeat 3-week cycles every 28 days (336).

Single-Agent Regimens

Gemcitabine

Gemcitabine: 1,000 mg/m² IV weekly for 7 weeks, then 1 week rest, subsequent cycles 1,000 mg/m² IV weekly for 3 weeks with 1 week rest

Repeat 3-week cycle every 28 days (337).
or

Gemcitabine: 1,000 mg/m² IV over 100 min at 10 mg/m²/min on days 1, 8, and 15

Repeat cycle every 28 days (338).

Capecitabine

Capecitabine: 1,250 mg/m² PO bid on days 1–14

May decrease dose to 850–1,000 mg/m² PO bid on days 1–14 to reduce the risk of toxicity without compromising clinical efficacy.

Repeat cycle every 21 days (339).

PROSTATE CANCER

Combination Regimens

Flutamide + Leuprolide (340)

Flutamide: 250 mg PO tid

Leuprolide:	7.5 mg IM every 28 days or 22.5 mg IM every 12 weeks

Flutamide + Goserelin (341)

Flutamide:	250 mg PO tid
Goserelin:	10.8 mg SC every 12 weeks

Estramustine + Etoposide

Estramustine:	15 mg/kg/day PO in 4 divided doses on days 1–21
Etoposide:	50 mg/m^2/day PO in 2 divided doses on days 1–21

Repeat cycle every 28 days (342).

Estramustine + Vinblastine

Estramustine:	600 mg/m^2 PO daily on days 1–42
Vinblastine:	4 mg/m^2 IV weekly for 6 weeks

Repeat cycle every 8 weeks (343).

Paclitaxel + Estramustine

Paclitaxel:	120 mg/m^2 IV continuous infusion on days 1–4
Estramustine:	600 mg/m^2 PO daily, starting 24 hours before paclitaxel

Repeat cycle every 21 days (344).

Mitoxantrone + Prednisone

Mitoxantrone:	12 mg/m^2 IV on day 1
Prednisone:	5 mg PO bid daily

Repeat cycle every 21 days (345).

Docetaxel + Estramustine

Docetaxel:	35 mg/m^2 IV on day 2 of weeks 1 and 2
Estramustine:	420 mg PO for the first 4 doses and 280 mg PO for the next 5 doses on days 1–3 of weeks 1 and 2

Repeat cycle every 21 days (346). Decadron is administered at 4 mg PO bid on days 1–3 of weeks 1 and 2.

Docetaxel + Prednisone

Docetaxel: 75 mg/m^2 IV on day 1

Prednisone: 5 mg PO daily

Repeat cycle every 21 days for up to a total of 10 cycles (347).

Single-Agent Regimens

Paclitaxel

Paclitaxel: 135–170 mg/m^2 IV as a 24-hour infusion on day 1

Repeat cycle every 3 weeks (348).
or

Paclitaxel: 150 mg/m^2 IV as a 1-hour infusion weekly for 6 weeks

Repeat cycle every 8 weeks (349).

Docetaxel

Docetaxel: 75 mg/m^2 IV on day 1

Repeat cycle every 21 days (350).
or

Docetaxel: 20–40 mg/m^2 weekly for 3 weeks

Repeat cycle every 4 weeks (350).

Estramustine

Estramustine: 14 mg/kg/day PO in 3–4 divided doses (351)

Goserelin

Goserelin: 3.6 mg SC on day 1

Repeat cycle every 28 days (352).

or

Goserelin: 10.8 mg SC on day 1

Repeat cycle every 12 weeks (352).

Leuprolide

Leuprolide: 7.5 mg IM on day 1

Repeat cycle every 28 days (353).

or

Leuprolide: 22.5 mg IM on day 1

Repeat cycle every 12 weeks (354).

Bicalutamide

Bicalutamide: 50 mg PO bid

In patients refractory to other antiandrogen agents, may start with a higher dose of 150 mg PO daily (355).

Flutamide

Flutamide: 250 mg PO tid (356)

Nilutamide

Nilutamide: 300 mg PO on days 1–30, then 150 mg PO daily (357)

Prednisone

Prednisone: 5 mg PO bid (345)

Ketoconazole

Ketoconazole: 1,200 mg PO daily (358)

Aminoglutethimide

Aminoglutethimide: 250 mg PO qid, if tolerated may increase to 500 mg PO qid (359)

RENAL CELL CANCER

Combination Regimens

Interferon-α + IL-2

Interferon α-2a: 9 million units SC on days 1–4, weeks 1–4

Interleukin-2: 12 million units SC on days 1–4, weeks 1–4

Repeat cycle every 6 weeks (360).

5-Fluorouracil + Gemcitabine

5-Fluorouracil:	150 mg/m²/day IV continuous infusion on days 1–21
Gemcitabine:	600 mg/m² IV on days 1, 8, and 15

Repeat cycle every 28 days (361).

Single-Agent Regimens

Low-dose IL-2

Interleukin-2:	3 million units/day IV continuous infusion on days 1–5

Repeat cycle every 14 days for 1 month (362).

Interferon-α

Interferon α-2a:	5–15 million units SC daily or 3–5 times per week (363)

SOFT TISSUE SARCOMAS

Combination Regimens

AD

Doxorubicin:	15 mg/m²/day IV continuous infusion on days 1–4
Dacarbazine:	250 mg/m²/day IV continuous infusion on days 1–4

Repeat cycle every 21 days (364).

MAID

Mesna:	2,500 mg/m²/day IV continuous infusion on days 1–4
Doxorubicin:	20 mg/m²/day IV continuous infusion on days 1–3
Ifosfamide:	2,500 mg/m²/day IV continuous infusion on days 1–3
Dacarbazine:	300 mg/m²/day IV continuous infusion on days 1–3

Repeat cycle every 21 days (365).

CYVADIC

Cyclophosphamide:	500 mg/m^2 IV on day 1
Vincristine:	1.5 mg/m^2 IV on day 1 (maximum, 2 mg)
Doxorubicin:	50 mg/m^2 IV on day 1
Dacarbazine:	750 mg/m^2 IV on day 1

Repeat cycle every 21 days (366).

CAV alternating with IE (Ewing's sarcoma)

Cyclophosphamide:	1,200 mg/m^2 IV on day 1
Doxorubicin:	75 mg/m^2 IV on day 1
Vincristine:	2 mg IV on day 1
and	
Ifosfamide:	1,800 mg/m^2 IV on days 1–5
Etoposide:	100 mg/m^2 IV on days 1–5

Alternate CAV with IE every 21 days for a total of 17 cycles (367)

Single-Agent Regimens

Doxorubicin

Doxorubicin:	75 mg/m^2 IV on day 1

Repeat cycle every 21 days (366).

Gemcitabine

Gemcitabine:	1,000 mg/m^2 IV weekly for 7 weeks, then 1 week rest Subsequent cycles 1,000 mg/m^2 IV weekly for 3 weeks with 1 week rest

Repeat 3-week cycle every 28 days (368).

Imatinib

Imatinib:	400 mg/day PO

Continue treatment until disease progression (159).

TESTICULAR CANCER

Adjuvant Therapy

PEB

Cisplatin:	20 mg/m² IV on days 1–5
Etoposide:	100 mg/m² IV on days 1–5
Bleomycin:	30 U IV on days 2, 9, and 16

Repeat cycle every 28 days for a total of 2 cycles (369). Adjuvant therapy of stage II testicular cancer treated with orchiectomy and retroperitoneal lymph node dissection.

Advanced Disease

BEP

Bleomycin:	30 U IV on days 2, 9, and 16
Etoposide:	100 mg/m² IV on days 1–5
Cisplatin:	20 mg/m² IV on days 1–5

Repeat cycle every 21 days (370).

EP

Etoposide:	100 mg/m² IV on days 1–5
Cisplatin:	20 mg/m² IV on days 1–5

Repeat cycle every 21 days (371).

PVB

Cisplatin:	20 mg/m² IV on days 1–5
Vinblastine:	0.15 mg/kg IV on days 1 and 2
Bleomycin:	30 units IV on days 2, 9, and 16

Repeat cycle every 21 days (372).

VAB-6

Vinblastine:	4 mg/m² IV on day 1
Dactinomycin:	1 mg/m² IV on day 1
Bleomycin:	30 U IV on day 1, then 20 U/m² continuous infusion on days 1–3

Cisplatin:	20 mg/m² IV on day 4
Cyclophosphamide:	600 mg/m² IV on day 1

Repeat cycle every 21 days (373).

VeIP (salvage regimen)

Vinblastine:	0.11 mg/kg IV on days 1 and 2
Ifosfamide:	1,200 mg/m² IV on days 1–5
Cisplatin:	20 mg/m² IV on days 1–5
Mesna:	400 mg/m² IV, given 15 minutes before first ifosfamide dose, then 1,200 mg/m²/day IV continuous infusion for 5 days

Repeat cycle every 21 days (374).

VIP (salvage regimen)

Etoposide (VP-16):	75 mg/m² IV on days 1–5
Ifosfamide:	1,200 mg/m² IV on days 1–5
Cisplatin:	20 mg/m² IV on days 1–5
Mesna:	400 mg/m² IV, given 15 minutes before first ifosfamide dose, then 1,200 mg/m²/day IV continuous infusion for 5 days

Repeat cycle every 21 days (374).

THYMOMA

CAP

Cyclophosphamide:	500 mg/m² IV on day 1
Doxorubicin:	50 mg/m² IV on day 1
Cisplatin:	50 mg/m² IV on day 1

Repeat cycle every 21 days (375).

Cisplatin + Etoposide

Cisplatin:	60 mg/m² IV on day 1
Etoposide:	120 mg/m² IV on days 1–3

Repeat cycle every 21 days (376).

ADOC

Cisplatin:	50 mg/m² IV on day 1

Doxorubicin: 40 mg/m² IV on day 1

Vincristine: 0.6 mg/m² IV on day 3

Cyclophosphamide: 700 mg/m² IV on day 4

Repeat cycle every 28 days (377).

THYROID CANCER

Combination Regimens

Doxorubicin + Cisplatin

Doxorubicin: 60 mg/m² IV on day 1

Cisplatin: 40 mg/m² IV on day 1

Repeat cycle every 21 days (378).

Single-Agent Regimens

Doxorubicin

Doxorubicin: 60 mg/m² IV on day 1

Repeat cycle every 21 days (378).

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