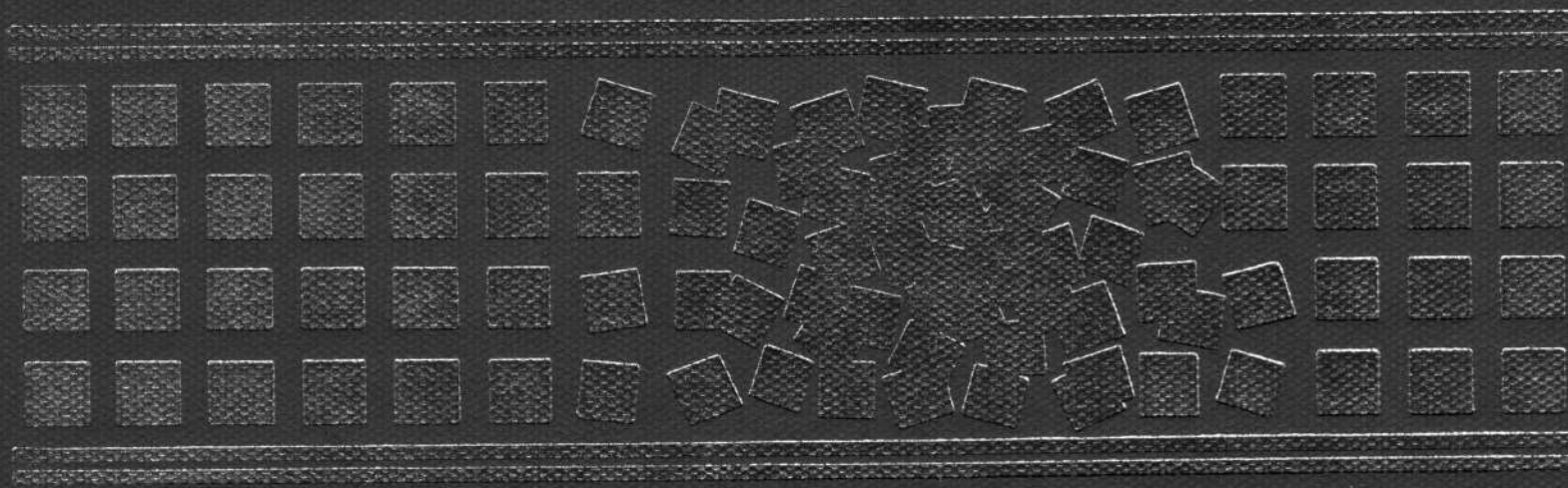
CANCER

Principles & Practice of Oncology



4th Edition

Vincent T. DeVita, Jr.
Samuel Hellman
Steven A. Rosenberg

J. B. Lippincott Company

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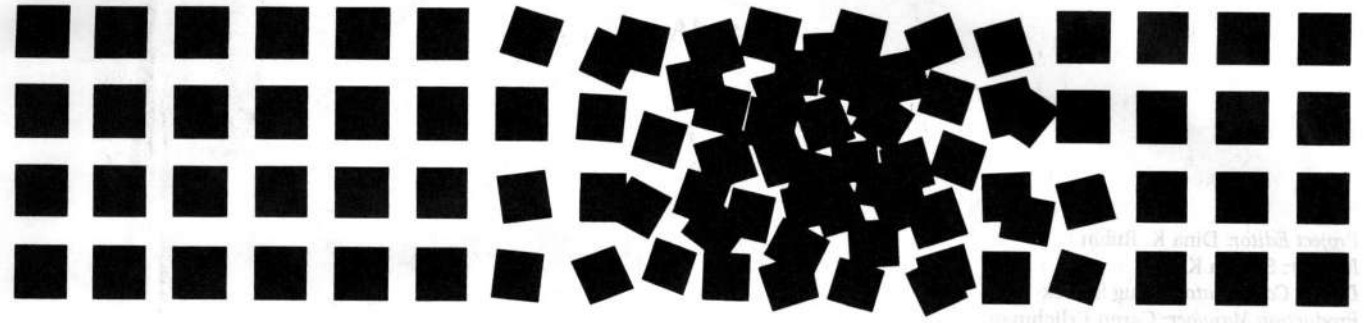

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The authors and publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accord with current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new or infrequently employed drug.

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Vincent T. DeVita, Jr

CHAPTER **16**

Principles of Chemotherapy

HISTORY

Cancer chemotherapy had its roots in the work of Paul Ehrlich, who coined the word chemotherapy. Ehrlich's use of rodent models of infectious diseases to develop antibiotics led George Clowes, at Roswell Park Memorial Institute in Buffalo, New York, in the early 1900s, to develop inbred rodent lines that could carry transplanted tumors.[1] These types of models served as the testing ground for potential cancer chemotherapeutic agents and only recently have been effectively supplemented by human cells grown in culture. Alkylating agents, the first modern chemotherapeutic agents, were a product of the secret war gas program in both world wars. An explosion in Bari Harbor during World War II[2,3] and the exposure of seamen to mustard gas led to the observation that alkylating agents caused marrow and lymphoid hypoplasia, which led to their use in humans with hematopoietic neoplasms such as Hodgkin's disease and lymphocytic lymphomas, first attempted at Yale-New Haven Medical Center in 1943. Because of the secret nature of the gas warfare program, this work was not published until 1946.[1,4] The demonstration of dramatic regressions in advanced lymphomas with chemicals caused much excitement and later much disappointment, because the tumors invariably grew back. After Farber's observation on the effects of folic acid on leukemic cell growth in children with lymphoblastic leukemia and the development of the folic acid antagonists as cancer drugs, the chemotherapy of cancer began in earnest. The cure of childhood leukemias and Hodgkin's disease with combination chemotherapy in the 1960s proved that human cancers, even in their advanced stages, could be cured by drugs, and the application to the chemotherapy of solid tumors began.

CHEMOTHERAPY AS PART OF THE INITIAL TREATMENT OF CANCER

There are four ways chemotherapy is generally used[5]: as an induction treatment for advanced disease, as an adjunct to the local methods of treatment, as the primary treatment for patients who present with localized cancer, and by direct installation into sanctuaries or by site-directed perfusion of specific regions of the body most affected by the cancer.

The term *induction chemotherapy* has been used to describe the drug therapy given as the primary treatment for patients who present with advanced cancer for which no alternative treatment exists.[6] Development of new treatments is based on the effectiveness of the cancer drugs in rodent models. Combinations of drugs are fashioned based on the effectiveness, the level of cross-resistance, and the limiting toxicity of the available drugs when used alone in similar patient populations. Patients who fail after one drug treatment and require further chemotherapy pose a particularly difficult treatment problem because of the volume of tumor, their poor general health, and drug resistance. Induction chemotherapy in these patients is referred to as *salvage treatment.*

Adjuvant chemotherapy denotes the use of systemic treatment after the primary tumor has been controlled by an alternative method, such as surgery and radiotherapy. The selection of an adjuvant treatment program for a particular patient is based on response rates in separate groups of patients with advanced cancers of the same histologic type. The determination of a population of patients as suitable for adjuvant treatment is based on available data on their average

risk of recurrence after local treatment alone and on disease variables known to influence prognosis adversely.

Primary chemotherapy denotes the use of chemotherapy as the initial treatment for patients who present with localized cancer for which there is an alternative, but less than completely effective, treatment. This approach also has been called *neoadjuvant chemotherapy*, but the term *primary chemotherapy* is more accurate.[7,8] For chemotherapy to be used as the primary treatment of a partially curable, localized cancer, there must be considerable evidence for the effectiveness of the drug program against advanced disease of the same type.

CLINICAL ENDPOINTS IN EVALUATING RESPONSE TO CHEMOTHERAPY

INDUCTION CHEMOTHERAPY

In induction chemotherapy for advanced cancer, it is possible to determine the response to drugs on a case-by-case basis. The partial response rate is usually defined as the fraction of patients that demonstrates at least a 50% reduction in measurable tumor mass; such responses usually are not of much value clinically, because they usually are brief and offset by the drug toxicity associated with continuous treatment. However, partial responses are useful in the evaluation of new drugs, or new drug programs, to determine whether the particular experimental approach is worth pursuing further. *The most important indicator of the effectiveness of chemotherapy is the complete response rate—it is the prerequisite for cure.* When new programs consistently produce more than an occasional complete remission, they have invariably later proved of practical value in medical practice. The qualitative and quantitative differences in the clinical value between a complete and a partial response are such that complete 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 all treatment is discontinued. This criteria is the only clinical counterpart of the quantifiable cytoreductive effect of drugs in rodent systems. A current trend among many clinical investigators is the use of "freedom from progression" of patients who have attained complete and partial responses, measured as a combined group.[8] This method is said to be an indicator of the practical potential of a new treatment, but 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 endpoints, such as median response duration and median survival, are also of little practical value until treatment results have been refined so that the complete response rate is higher than 50%.

ADJUVANT CHEMOTHERAPY

There was great excitement concomitant with the use of chemotherapy as an adjunct to local treatments. The promise was great, because tumor volume is at a minimum when adjuvant therapy is initiated, and it was assumed that treatment with drugs at this stage would produce a much higher cure rate or that treatment intensity could be reduced and side effects thereby diminished, without loss of therapeutic effectiveness. Both assumptions have little scientific basis. Failure to appreciate the problems surrounding the assessment of the response of a group of patients to adjuvant chemotherapy is the source of some of the current disillusionment with the positive, but less than dramatic, results achieved with adjuvant chemotherapy in common tumors, such as breast and colorectal cancers.[9,10]

It should be remembered that the major indicator of effectiveness of a chemotherapy program—the complete remission rate—is lost in the adjuvant setting, because the primary tumor has already been removed. In the clinic, treatment is selected for individual patients based on response rates in an entirely different population of patients with advanced disease with the same histologic type. Relapse-free survival remains the major endpoint, but the micrometastases in the population of adjuvant-treated patients consist of a mixture of tumor cells, some of which can be expected to be sensitive to chemotherapy, and others resistant. The relapse-free survival in the adjuvant setting, therefore, measures time to regrowth of cells unresponsive, partially responsive, or very sensitive to chemotherapy and is the equivalent of the duration of remission of complete and partial responders and the interval of regrowth in patients who would have been classified as nonresponders. In this sense, it is similar to the use of freedom from progression in patients with advanced disease. Attempts to use in vitro assays of drug sensitivity from the biopsy material of primary tumors to overcome the shortcomings of the absence of an indicator of individual response have not proved practical.

PRIMARY CHEMOTHERAPY

The unique feature of using chemotherapy in patients with localized tumor, before or instead of purely local treatments, is the preservation of the presenting tumor mass as a biologic marker of responsiveness to the drugs. As with induction chemotherapy for patients with advanced cancer, it is possible to determine, on a case-by-case basis, the potential effectiveness of a new treatment program. By definition, the presenting tumor mass is also the largest aggregate of tumor in the body and, historically, the oldest, and it is therefore the aggregate mass of tumor cells most likely to contain one or more resistant cell lines.[11] Being the largest mass of cells, it is also the mass with the least favorable cell kinetics. It is reasonable to assume, then, that whatever the effect of chemotherapy the physician sees on the primary tumor, a similar or greater effect is occurring fairly uniformly in micrometastatic deposits. A poor response of the primary tumor to chemotherapy indicates a group of patients for which alternative methods of treatment should be used quickly. Another feature of primary chemotherapy is the ability to delineate partial responders with varying degrees of prognosis, as determined by the state of the residual tumor mass after an initial good but partial response. Removal of residual tumor and histologic examination of the tissue allow determination of the viability of the remaining tumor mass. The response duration of complete and partial responders must be catalogued separately.

The most important issue facing investigators of primary chemotherapy is whether an effective primary chemotherapy treatment, pursued flexibly and intensively to complete remission, plus two or more additional cycles of treatment, will define a significant fraction of patients whose disease is cured

by chemotherapy alone, without the addition of alternative treatments. In carefully selected patients with some stages of the commonest tumors for which there is less than satisfactory standard treatment, such studies are ethically and theoretically sound and are being pursued. Such an approach could result in briefer, less morbid, and more effective treatment programs.[5]

The use of chemotherapy as the primary treatment is reviewed, when appropriate, in each of the disease-oriented chapters. Table 16–1 lists tumors in which primary chemotherapy for localized forms of the cancer in question have already been incorporated in clinic protocols (first and second categories) and in which current clinical trials show considerable progress (third category).[12–17]

SPECIAL USES OF CHEMOTHERAPY

Special uses of chemotherapy include (1) the installation of drugs into the spinal fluid, directly through a lumbar puncture needle or into an implanted Ommaya reservoir, to treat meningeal leukemia and lymphoma, and into the pleural or the pericardial space to control effusions; (2) splenic infusion to control spleen size; (3) hepatic artery infusion to treat hepatic metastases selectively; (4) carotid artery infusion to treat head and neck cancers and brain tumors; and (5) intraperitoneal installation of drugs using dialysis techniques. These uses are discussed throughout this book in relation to specific cancers. In all instances, the rationale for directed chemotherapy is based on achieving a higher concentration over time ($C \times T$) against the target tumor tissue while sparing normal tissue. The usefulness of intracerebrospinal fluid and intrapleural administration of drugs is already established. Hepatic infusion of chemotherapy has been simplified and improved enough by the development of technology for the infusion of drugs that a reevaluation of this approach is justified (see Chap. 61, section 3). It is now possible to measure the active principles of cancer drugs and their targets within the biologic range, and drugs can be infused in timing with the body's circadian rhythm (see Chap. 69, section 7).

The intraperitoneal administration of drugs to treat ovarian cancer, a disease that kills almost exclusively by local effects in the abdomen, is now being investigated, because it allows a wide distribution of antitumor drugs in the smallest interstices of the abdominal cavity, and because a higher $C \times T$ at the tumor is achieved (see Chaps. 18 and 39).[18,19] The concentration of drug available in the peritoneal cavity for some drugs with this "belly bath" technique far exceeds the plasma level achievable with systemic administration. The effects are particularly marked for drugs such as 5-fluorouracil, which is metabolized in the liver and excreted by the kidney, and doxorubicin and cisplatin, which, because of their molecular size, diffuse more slowly across the peritoneal membrane. A similar approach is being explored with abdominal installation of photoaffinity compounds, with subsequent exposure to laser light sources (see Chap. 69, section 7).

Drugs can also be encompassed in lipid bilayer droplets called *liposomes*.[20–22] The surface characteristics of liposomes can be altered to direct their delivery to specific organ sites or into resistant cell lines. Labile liposomes that dissolve at temperatures of 41°C can deposit drugs selectively in preheated areas.[21] A disadvantage of liposomes, however, is their failure to leave the vascular system except in the sinusoids of the liver and the spleen; liposome encapsulation of drugs for targeted delivery has been of limited value.[22]

TABLE 16–1. Primary Chemotherapy

Neoplasms in Which Chemotherapy Is the Primary Therapeutic Modality
Localized diffuse large cell lymphoma
Burkitt's lymphoma
Childhood Hodgkin's disease
Wilms' tumor
Embryonal rhabdomyosarcoma
Small cell lung cancer
Neoplasms in Which Primary Chemotherapy Can Allow Less Mutilating Surgery
Anal carcinoma
Bladder carcinoma
Breast cancer
Laryngeal cancer
Osteogenic sarcoma
Soft tissue sarcomas
Neoplasms in Which Clinical Trials Indicate an Expanding Role for Primary Chemotherapy in the Future
Non-small-cell lung cancer
Breast cancer
Esophageal cancer
Nasopharyngeal cancer
Other cancers of the head and neck region

PRINCIPLES GOVERNING THE USE OF COMBINATION CHEMOTHERAPY

With some exceptions (*e.g.*, choriocarcinoma and Burkitt's lymphoma), single drugs do not cure cancer. It became apparent in the 1960s that drug combinations are necessary to produce durable clinical responses. In the early years of chemotherapy, drug combinations were developed based on known biochemical actions of available anticancer drugs rather than on their clinical effectiveness. These programs were largely ineffective.[23–27] The era of effective combination chemotherapy began when an array of active drugs from different classes became available for use in combination in the treatment of leukemias and lymphomas. Combination chemotherapy has now been extended to the treatment of most other malignancies, as described throughout this text.

Combination chemotherapy accomplishes three important objectives not possible with single-agent treatment. It provides maximal cell kill within the range of toxicity tolerated by the host for each drug; it provides a broader range of coverage of resistant cell lines in a heterogenous tumor population; and it prevents or slows the development of new resistant lines.

The following principles have been useful in the selection of drugs in the most effective drug combinations, and they guide the development of new programs:

1. Only drugs known to be partially effective when used alone should be selected for use in combination. If avail-

able, drugs that produce some fraction of complete remission are preferred to those that produce only partial responses.

2. 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 and more general discomfort for the patient, 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.
3. Drugs should be used in their optimal dose and schedule.
4. Drug combinations should be given at consistent intervals. 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.

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. Also, arbitrarily reducing the dose of an effective drug to add other less effective drugs may reduce the dose of the most effective agent below the threshold of effectiveness and destroy the capacity of the combination to cure that particular patient.

Bone marrow has a storage compartment that can supply mature cells to the peripheral blood for 8 to 10 days after the stem cell pool has been damaged by cytotoxic drugs. Events measured in the peripheral blood are usually a week behind events occurring in the bone marrow. In previously untreated patients, leukopenia and thrombocytopenia are discernible on the ninth or tenth day after initial dosing. Nadir blood counts are noted between days 14 to 18, with recovery apparent by day 21 and usually complete by day 28. Prior treatment with drugs or x-radiation may alter this sequence by depleting the stem cell pool, shortening the time to the appearance of leukopenia and thrombocytopenia, and prolonging the recovery time. Curiously, when the second half of a combination given in the clinic on a day 1, day 8 schedule is omitted, leukopenia and thrombocytopenia comparable with that seen with the full combination usually occur, suggesting that the second set of doses does not cause an equal increment in bone marrow suppression, possibly because the stem cell compartment is still in a quiescent state. This result also suggests that, in most instances, the day-8 doses can be given safely, even if leukopenia and thrombocytopenia have already become evident. The interval of greatest importance in the clinic is the duration of the nadir level of leukocytes and platelets. The highest risk of infection or bleeding occurs with granulocyte counts lower than 500/dl and platelet counts lower than 20,000/dl. If this nadir lasts only 4 to 7 days, it is tolerated by most patients without supplemental support. Increasing doses of most anticancer drugs, within the range of the maximally tolerated dose, usually does not ablate the marrow or even prolong the time to recovery. Repeated dosing during the phase of early recovery of the marrow (days 16–21), however, may cause severer toxicity in the second treatment cycle in patients whose marrow is not the source of, or involved with, the tumor.

These types of data led to the familiar 2-week interval between cycles of the most effective drug combinations (new cycles begin on day 28 after the first dose) to accommodate the recovery time of human bone marrow. Although this treatment schedule is suitable for some tumors, the regrowth characteristics of others, such as diffuse large cell lymphomas, Burkitt's lymphoma, and leukemia, often permit the tumor volume to return to pretreatment levels in the interval required for bone marrow recovery, and other approaches to cycling drug combinations are now being explored. One such approach has been to use non-marrow-toxic chemotherapeutic agents, cycled with marrow-toxic agents, to permit the bone marrow to recover despite continuous treatment. This method has been useful in patients with rapidly growing diffuse large cell lymphomas. It is limited by the sensitivity of the tumor in question to the available non-marrow-toxic agents. The availability of colony-stimulating factors as supportive tools (see Chap. 62, section 2) is altering the design of clinical trials as well. Colony-stimulating factors have been coupled with cytotoxic combination chemotherapy, and the nadir leukopenia can usually be avoided or ameliorated.[28–32]

IMPACT OF THE GOLDIE-COLDMAN HYPOTHESIS ON DESIGN OF CLINICAL TRIALS USING COMBINATION CHEMOTHERAPY

In 1943, Luria and Delbruck described a principle in bacterial genetics important to our understanding of the development of spontaneous resistance to cancer chemotherapy that led to a reconsideration of how chemotherapy was used in clinical trials.[33] They 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. In 1979, Goldie and Coldman applied this principle to the development of resistance by cancer cells to anticancer drugs without prior exposure to these drugs.[34] They proposed that the nonrandom cytogenic 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.[35] 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 and that these events would begin to occur at population sizes between 10^3 and 10^6 tumor cells (1000–1 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 is newly diagnosed would be a function of the mutation rate and the size of the tumor. If the mutation rate is as infrequent as 10^{-6}, a tumor composed of 10^9 cells (a 1-cm mass) would still be certain 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 clinic, such tumors should initially respond to treatment with a complete or partial remission, but then recur as the resistance clone(s) expanded to repopulate the mass or masses. Such a pattern is seen with the use of chemotherapy in many drug-responsive cancers in the clinic.

The Goldie-Coldman hypothesis, therefore, predicts that

resistance should be a problem even with small tumor burdens, and the maximal chance for cure occurs when all available effective drugs are given simultaneously.[34] Because this would involve using 8 to 12 drugs simultaneously, this approach has not been tested in the clinic because of the fear that the use of more than five cytotoxic drugs, at full doses, would not be possible. The alternative approach, using two programs of equally effective, noncross-resistant drug combinations in alternating cycles, has been under evaluation for more than 10 years. Unfortunately, many studies purporting to test the Goldie-Coldman hypothesis have been poorly designed. In many instances, inadequate testing has been done to determine whether the alternate combination is truly noncross-resistant and as equally effective as the primary treatment (in most instances, it is not),[1] which it must be to fulfill the hypothesis as described by Goldie and Coldman. Second, dosing is rarely controlled, so that doses of essential drugs are modified downward, a priori, without testing the impact of such dose reductions on outcome. A more recent approach is the use of half of the drugs of each of the effective combination on days 1 and 8, respectively (so-called hybrid combinations). This approach is being tried in patients with Hodgkin's disease and diffuse large cell lymphomas. The use of alternating cycles of combination chemotherapy has not yet proved to be significantly more effective than are full doses of a single effective combination program.

In 1986, Day reanalyzed the Goldie-Coldman hypothesis and relaxed the requirement for symmetry in the model.[36,37] Although his model verified the basic tenets of the Goldie-Coldman hypothesis, it suggested a different approach to sequencing combinations: In many instances, the sequential use of combinations should out-perform alternating cycles, because no two combinations are likely to be strictly noncross-resistant or have equal cell killing capacity, the symmetry assumed by Goldie and Coldman. Day formulated "the worst-drug rule," which refers to any strategy using more or earlier doses of a treatment that is the least effective of two or more available options.[38] The worst-drug rule has interesting implications. First, it is a nonintuitive approach. If two treatments are available, treatments A and B, and B is known to be better, a physician is more likely to use B first. However, cells that are resistant to the best treatment, B, must be eliminated by the weaker program, A, and because it is the weaker program, one cannot wait too long to use it or the overgrowth of the population resistant to B will place the physician and patient in a situation difficult to overcome. The model predicts that, if six cycles of A and B are planned, using the weaker program—A—first performs better. There have been clinical examples in which sequential therapies have outperformed alternating cyclical use of the same programs if the dose intensity of the two regimens is carefully controlled.[39]

No rigid schedule can accommodate all the variables assumed to be important for maximum effectiveness of combination chemotherapy and the requirements of the patients in the practice of medical oncology. Physicians must often adjust doses at intervals to administer drugs safely. 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 major reductions in the capacity to attain a complete remission in patients with drug-responsive tumors.[38] The physician and the patient must consider the risk of dying from cancer prematurely compared with the transient benefits of reducing the acute side effects of treatment. Adhering to the standard sliding scale for dose adjustments, usually published with most new treatments, is the most appropriate way to make the necessary adjustments without compromising long-term outcome. In addition to providing guidelines for dose reduction, these sliding scales provide consistency between patients, and between studies, by preserving the intervals between cycles and the integrity of each drug combination. These alternatives and their potential impact on the quality and quantity of life should be made clear to patients as part of the informed consent process if they are to share intelligently in decisions about dose modifications made by their physicians.[40]

RESPONSE TO CHEMOTHERAPY IS AFFECTED BY THE BIOLOGY OF TUMOR GROWTH

In the early 1960s Skipper and colleagues identified the guiding principles of present-day chemotherapy, using the rodent leukemia L1210 as a model.[41–43] Applying these principles to the drug treatment of human cancers required an understanding of the differences not only between the growth characteristics of this rodent leukemia and of human cancers but also in growth rates of normal target tissues in mice and humans. For example, L1210 leukemia is a rapidly growing tumor 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 of its cells are actively progressing through the cell cycle), its life cycle is consistent and predictable.[44]

The relation between cell number and survival in L1210 leukemia is linear, as shown in Figure 16–1. The time to death of animals bearing L1210 leukemia is the interval required to achieve a population size of about 10^9 (1 billion) cells. With a growth fraction of 100% and a doubling time of 12 hours, 10^9 cells accumulate by 19 days after the injection of a single cell, by 10 days after the injection of 10^5 cells, and by 5 days after the administration of 10^8 cells. Skipper and associates postulated that the increase in host lifespan after cytotoxic chemotherapy of L1210 leukemia was largely due to the cytocidal effect of treatment on the tumor cell population. In these early elegant mouse experiments, they calculated the residual number of cells after treatment by extrapolating back from the duration of prolongation of life after a single treatment. An increase of 2 days in life would be equivalent to a 90% destruction of tumor cells (a 1-log kill), or a reduction in the cell number from 10^6 to 10^5. A 99.999% destruction of tumor cells, a number that seems enormous to most clinicians, represents only a 5-log kill and does not cure animals unless the initial inoculum is small, perhaps 10^4 cells or fewer. If multiple treatments are given, the net tumor cell kill per treatment is the sum of the surviving cells plus the regrowth of the tumor cell population before the next treatment.

The killing effects of cancer drugs in this model tumor follow log-kill kinetics, that is, if a particular dose of an individual drug kills three logs of cells and reduces tumor burden from

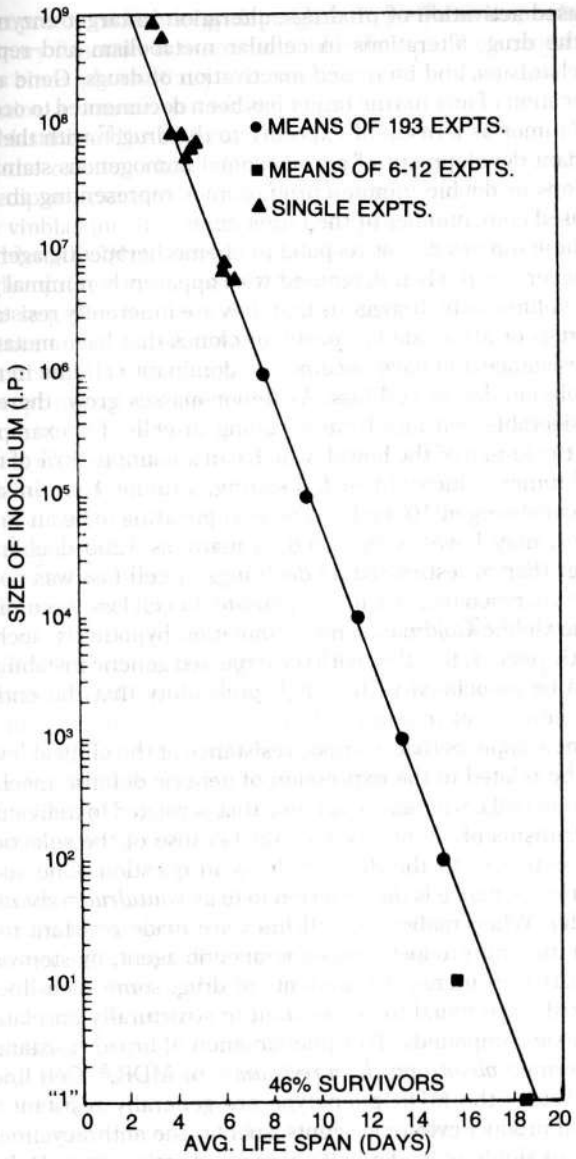

FIGURE 16–1. Relation between size of tumor cell inoculation and time to death of the host in L1210 leukemia in CDF_1 mice.

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. The cell kill, therefore, is proportional, regardless of tumor burden. This model fits the response of L1210 murine leukemia to chemotherapy. When treatment failed in the experiments of Skipper and colleagues, it was because the initial tumor burden was too high to allow the delivery of curative doses of chemotherapy to eradicate the last leukemia cell. The cardinal rule of chemotherapy—the invariable inverse relation between cell number and curability—was established in this model and applies to all others. Skipper and colleagues proceeded to show that with an understanding of these basic facts, this rodent leukemia could be cured by specifically designed doses and schedules tied to tumor volume and growth characteristics.[41]

Although murine leukemias seemed to follow exponential kinetics, available data suggested that most human tumors did not appear to grow exponentially. For example, the concept of log kill would have predicted that some large tumors in the clinic should have been more sensitive to treatment than has been experienced. In toto, the available data in human 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 about 37% of its maximum size. In a 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 depends on where the tumor is in its growth curve. Gompertzian-growing tumors will respond to cytotoxic drugs in a Gompertzian fashion. Therefore, predictions can also be made about the behavior of small tumors, such as tumor burdens that might be present after primary surgical therapy. When the tumor is clinically undetectable, its growth fraction would be at its largest 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 higher than it would be later in the tumor course. This observation initially was used to justify dose reductions at lower tumor volumes, which may account for some of the disappointment in the outcome of adjuvant studies in breast cancer, because there is no scientific justification for such dose reductions if residual cancer cells survive the treatment. The Gompertzian growth model is important for another reason: It impacts on the patterns of regrowth of residual tumor cells. In breast cancer, Norton has analyzed data from multiple adjuvant studies and also the only available studies of untreated patients who presented with localized cancers who were followed until death.[37,38,45,46] He found that in all instances a Gompertzian growth model precisely fitted the growth curves of these tumors. In adjuvant situations, the model showed that relapse-free survival and survival curves cannot discriminate between residual cell populations of 1 or 1 million cells, because the regrowth of residual cell populations will be faster at smaller residual volumes than it will be at larger residual volumes, producing identical endpoints sometimes at 5 years after diagnosis. Therefore, the effect of dose alterations cannot be differentiated using standard assay systems of effectiveness. Experimental observations imply that there are kinetic reasons for the failure of chemotherapy to cure large tumors and for the inadequate assessment of the effectiveness of drug adjuvant treatment. The data imply that short of total eradication of micrometastases (cure), varying residual volumes produce similar 5-year relapse-free survival and obscure the deleterious effect of dose reductions. This information has been useful in the design of new adjuvant treatment protocols in breast cancer.

BIOCHEMICAL RESISTANCE TO CHEMOTHERAPY IS THE MAJOR IMPEDIMENT TO SUCCESSFUL TREATMENT

The cancer cell presents a variable and moving target for anticancer drugs. The interrelation of pharmacokinetics and

tumor and normal target cell kinetics is the fulcrum of clinical cancer chemotherapy. The therapeutic and toxic effects of chemotherapeutic agents are related to the time the active principle is exposed in an effective concentration to its target (Fig. 16–2). The same degree of cytotoxicity can be achieved, on different schedules, from the same concentration of drug multiplied by the time of exposure ($C \times T$). This relation obtains across different species when the drugs are metabolized and excreted in a similar fashion. This principle has made it possible to translate doses of drugs devised in animals to humans for early clinical testing.[47,48] A given concentration of drug multiplied by the time of exposure to its target ($C \times T$) generally is equally cytotoxic in populations of cells with equivalent growth characteristics and sensitivity to the agent(s) in question.

When the active principles of an anticancer drug reach their target, however, another obstacle to the capacity to kill the cancer cell appears: specific and permanent biochemical resistance to the drug. Resistance to drugs occurs de novo in cancer cells (intrinsic resistance) or is concomitant to exposure to drugs (acquired resistance).[48–57]

Many specific mechanisms of drug resistance have been revealed whereby cancer cells demonstrate the ability to circumvent a well-defined pathway of attack by an individual cytotoxic agent. These mechanisms are discussed in detail in Chapter 18 and are summarized in Figure 16–2.[49] Mechanisms of primary drug resistance include decreased uptake caused by changes in drug-specific transport mechanisms, decreased activation of prodrugs, alteration in target enzymes of the drug, alterations in cellular metabolism and repair mechanisms, and increased inactivation of drugs. Gene amplification of an enzyme target has been documented to occur in a tumor as a result of exposure to the drug,[57] with the attendant development of chromosomal homogenous staining regions or double-minute chromosomes representing an increased copy number of the target gene.

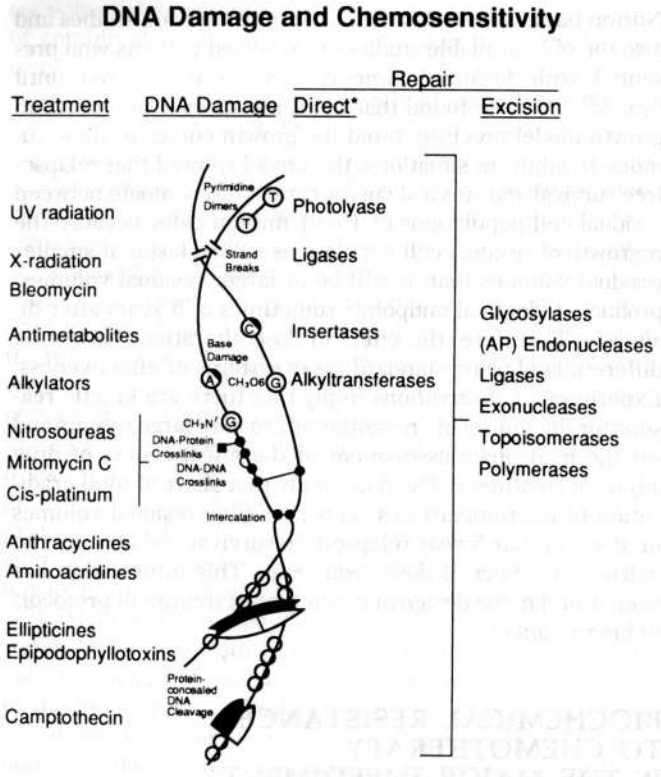

FIGURE 16–2. Schematic illustration of DNA damage and repair mechanisms in cells exposed to cytotoxic modalities. *Reversal/removal. AP, apurinic (apyrimidinic) site. (Epstein, RA. Drug-induced DNA damage and tumor chemosensitivity. J Clin Oncol 1990;8:2062–2084)

Some tumors do not respond to chemotherapeutic agents, however, even when diagnosed with apparently minimal tumor volume, which suggests that they are inherently resistant to drugs or are made up mostly of clones that have mutated to resistance and have become the dominant cell line in the population due to cell loss. As tumor masses grow, there is considerable cell loss from shedding of cells, for example, into the lumen of the bowel, which can amount to 90% of the total tumor volume. In such a setting, a tumor 1 cm in size and consisting of 10^9 cells, although appearing to be an early tumor, may have experienced as many as 1200 doublings rather than an estimated 32 doublings, if cell loss was not a factor, to reach that size to compensate for cell loss. According to the Goldie-Coldman somatic mutation hypothesis, such a kinetic history, together with the expected genetic instability, could be associated with a high probability that the entire mass consists of resistant cell lines.

It now appears that intrinsic resistance at the clinical level may be related to the expression of generic defense mechanisms in cells, whereas resistance that is related to individual mechanisms of action occurs later because of the selection after exposure to the drug or drugs in question. One such generic resistance is that referred to to as *multidrug resistance* (MDR). When malignant cell lines are made resistant to a single natural product chemotherapeutic agent, by stepwise incubation in increasing amounts of drug, some such lines, curiously, are found to be resistant to structurally unrelated cytotoxic compounds. This phenomenon of broad resistance was termed *pleiotropic drug resistance*, or MDR.[58] Cell lines that display the MDR phenotype are generally resistant to natural product cytotoxic agents, such as the anthracyclines, vinca alkaloids, epipodophyllotoxins, and actinomycin D. Because all these agents are believed to have different mechanisms of action, investigation of MDR has focused on the cell's basic defense mechanism against toxic agents that humans are exposed to naturally in the environment.

MDR has been shown to be associated with decreased intracellular drug accumulation and the presence of a 170-kd plasma membrane–associated glycoprotein (P-glycoprotein) that is not detectable in most parenteral drug-sensitive lines.[59,60] P-glycoprotein content has been directly correlated with the degree of the decrease in intracellular accumulation of the toxins and the drug resistance exhibited by the cell.[61,62] These observations suggest that the appearance of P-glycoprotein is associated with resistance perhaps by regulating the transport of toxins out of the cell. Most, but not all, cell lines with the MDR phenotype that have since been established show increased expression of the gene encoding P-glycoprotein, the *MDR* gene.[63–70] Recently, the gene for cystic fibrosis has been cloned and shown to produce a protein with marked homology to the P-glycoprotein, and additional data suggest that impaired drug influx may be a separate phenomenon. A great deal of evidence suggests that the P-

glycoprotein is an energy-dependent drug efflux pump, whose primary function is to extrude chloride ions. P-glycoprotein also binds photoaffinity analogs of the natural product vinblastine, a reaction that is competitively inhibited by unlabeled vinblastine and by anthracyclines.[68–72] Several agents, including the calcium channel blocker verapamil, quinidine, and nifedipine, can bind to the P-glycoprotein and compete with the vinblastine analogs for binding with the P-glycoprotein. Full-length cDNA sequences encoding the mouse and human P-glycoprotein gene have been isolated, and their nucleotide sequences determined. The deduced amino acid sequence of this protein shows structural similarities to a well-characterized bacterial membrane transport protein.[72–74] P-glycoprotein RNA expression has been found in high levels in normal adrenal gland and kidney tissue and in moderate levels in liver and colon tissue.[75] Recently, P-glycoprotein has been shown to be expressed on CD-34+ bone marrow stem cells, but not in more mature cells of the hematopoietic system, and in the endothelial lining of blood vessels. Both observations have important implications for the design of treatment protocols.[8,76,82] Because colon, kidney, and liver tissues are exposed to naturally occurring environmental toxins, the role of the P-glycoprotein in health may be one of protecting by facilitating efflux of these toxins or to serve as an alternative ion transport mechanism.

The range of expression of P-glycoprotein by human tumors is under intensive study.[77–79,82–84] In general, P-glycoprotein is highly expressed in tumors intrinsically resistant to chemotherapy and poorly expressed in drug-responsive tumors, unless they are sampled after relapse. These data provide avenues to pursue clinically. Protocols can be designed to use agents not affected by the pump in resistant tumors, or natural product anticancer drugs can be given early in the course of the disease, before MDR is expressed in most cells.[38] Agents that block the pump mechanism also can be used simultaneously with natural product anticancer drugs. These approaches are reviewed in reference 38 and in Chapter 69, section 6.

Another type of multidrug resistance often follows on the heels of that associated with the P-glycoprotein expression and is associated with the topoisomerase enzymes.[85–88] Topoisomerases are necessary for DNA replication, and they catalyze changes in the secondary and tertiary structures of DNA to relax DNA tension during transcription and cell division. Topoisomerase II appears to be the enzyme that is the target of antineoplastic drugs that act as DNA-intercalating agents, such as etoposide and the anthracyclines. The only known class of topoisomerase I-targeting drugs—the camptothecins—has shown unprecedented activity against human cancers in animal models and is currently undergoing clinical trials. Topoisomerases, therefore, may represent the final common pathway of cytotoxicity of several different classes of antineoplastic agents. Drugs that act through interaction with the topoisomerases do so by preventing the religation of DNA through the formation of cleavable complexes. Resistance may occur through alterations in production and function of the enzymes. For example, an etoposide-resistant Chinese hamster ovary cell line that was cross-resistant to the structurally dissimilar agents m-AMSA, mitoxantrone, and the anthracycline doxorubicin demonstrated altered topoisomerase II activity.[89] In addition, alteration in the topoisomerase I-like activity was found in Chinese hamster cells selected for resistance to elipticine and cross-resistance to m-AMSA and etoposide.[90]

As a result of these data, there is considerable excitement about the prospect of improving the effectiveness of chemotherapy by circumventing both types of MDR, by preventing the development of resistance or by interfering with the mechanisms themselves.

CONCEPT OF DOSE INTENSITY

For drug-sensitive cancers in favorable kinetic circumstances, the factor limiting the capacity to cure is proper 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 radiation therapy and chemotherapy, it is the difference between the dose-response curves of normal and tumor tissue that must be exploited during treatment. In experimental models, the dose-response curve is usually steep in the linear phase. Almost without exception in rodents bearing transplantable tumors, a reduction of doses in the linear phase of the dose-response curve results in a loss of the capacity to cure the tumor before there is a diminution in the response rate. That is, complete remissions will continue to be observed, but with dose reduction as small as 20%, the last few residual cells may not be eliminated, and relapse is inevitable. There is an extremely important lesson in these animal data for clinicians who, in their daily practice, judge the adequacy of their therapy by measuring the response rate of visible or palpable tumor masses and only much later are able to evaluate the treatment by survival results. This point is illustrated in Table 16–2, which summarizes data from numerous experiments conducted by Skipper and colleagues at the Southern Research Institute using the transplantable and palpable Ridgway osteosarcoma tumor model.[91,92] Reduction in the average dose intensity of the two-drug combination of L-phenylalanine mustard (L-PAM) and cyclophosphamide causes a marked decrease in the cure rate *before a significant reduction in the complete remission rate occurs*. On the average, a dose reduction of approximately 20% leads to a loss of 50% of the cure rate. The converse is also true. In high-growth-

TABLE 16–2. Ridgway Osteogenic Sarcoma: Response to Different Dose Intensity of Two-Drug Combination of Cyclophosphamide and L-PAM

	RDI			
CPA	*L-PAM*	*Average*	*% CR*	*% Cures*
0.38	0.82	0.60	100	60
0.75	0.18	0.47	100	44
0.25	0.55	0.44	100	10
0.50	0.12	0.31	10	0
0.17	0.36	0.27	0	0

RDI, relative dose intensity; CPA, cyclophosphamide; L-PAM, L-phenylalanine; CR, complete response. Tumors weighed 2–3 g.
(Modified from Skipper HE. Booklet No. 5. Birmingham: Southern Research Institute, 1986)

TABLE 16–3. Sample Calculations: Dose Intensity, Relative Dose Intensity, and Average Relative Dose Intensity

	Dose Intensity	*Relative Dose Intensity*
Calculation of Dose Intensity		
Test Schedule		
Cyclophosphamide 80 mg/m²/d (continuously)	560 mg/m²/wk	
Calculation of Relative Dose Intensity		
Standard		
Cyclophosphamide 80 mg/m²/d (continuously)	560 mg/m²/wk	
Test Schedule		
Cyclophosphamide 100 mg/m²/d (d 1–14, q 28 d)	350 mg/m²/wk	350/560 = 0.62
Calculation of Average Relative Dose Intensity		
Standard*		
Cyclophosphamide 2 mg/kg/d	560 mg/m²/wk	
Methotrexate 0.7 mg/kg/wk	28 mg/m²/wk	
5-Fluorouracil 12 mg/kg/wk	480 mg/m²/wk	
Test Regimen		
Cyclophosphamide 100 mg/m²/d (1–14)	350 mg/m²/wk	350/560 = 0.62
Methotrexate 40 mg/m²/d 1, 8	20 mg/m²/wk	20/28 = 0.71
5-Fluorouracil 600 mg/m²/d 1, 8	300 mg/m²/wk	300/480 = 0.62
Repeat cycles every 28 d		*Average* 0.65

* Assume standard regimen to be CMF. To convert mg/kg to mg/m², multiply by 40.
(Hryniuk WM: The importance of dose intensity in the outcome of chemotherapy. In: DeVita VT, Hellman S, Rosenberg SA, eds. Important advances in oncology. Philadelphia: JB Lippincott, 1988: 121–142)

fraction tumors, a twofold increase in dose often leads to a tenfold increase (1 log) in tumor cell kill. Although animal models are not the perfect analog for human cancers, the invariable nature of these data indicates that the general principle is transferable to the clinic and is ignored at great peril. Because anticancer drugs are toxic, it is often appealing to avoid acute, but not life-threatening, toxicity by diminishing the dose or increasing the intervals between cycles of treatment. This kind of ad hoc adjustment of dosing is probably the main reason for treatment failure in patients with *drug-sensitive human tumors* undergoing their first chemotherapy treatment.

It has been difficult to compare the impact of different dosing practices in treatment programs. Hryniuk and colleagues analyzed treatment outcome in a number of different tumors as a function of what they have termed *dose intensity*.[93–98] They defined dose intensity as the amount of drug delivered per unit of time, expressed as mg/m²/wk, regardless of the schedule or route of administration. Relative dose intensity (RDI) is the amount of drug delivered per unit of time relative to an arbitrarily chosen standard single drug, or, for a combination regimen, the decimal fraction of the ratio of the average dose intensity of all drugs of the test regimen compared with the standard regimen. A sample calculation of the RDI for a commonly used regimen, the cyclophosphamide, methotrexate, 5-fluorouracil (CMF) combination for breast cancer, is provided in Table 16–3.[94] To calculate the average RDI for a regimen containing fewer drugs than the standard regimen, a dose intensity of zero is assigned to the missing drug(s), and the average RDI of the test regimen is divided by the total number of drugs in the standard.[94] The dose intensity of various programs is compared over whatever time frame the treatment programs are administered. Calculations can be made of intended dose intensity, the dose intensity as described in the treatment protocol, or actual or received dose intensity. Received dose intensity calculations are more useful data because they reflect the impact of dose reductions and necessary treatment delays imposed in actual practice.

Because calculations are made based on the amount of drugs given per week, regardless of schedule, treatment delays are given equal weight with dose reductions. Calculations of the dose intensity, therefore, require the assumption that differences in scheduling does not influence treatment outcome. Although this first appears to be heretical, close scrutiny of all available data in humans and rodents shows that scheduling influences outcome mostly by affecting toxicity, in this way allowing higher doses to be administered over the same time frame. An example can be found in the use of methotrexate in rodents and humans. Daily administration of low doses of methotrexate is extremely toxic and severely limits the dose and duration of therapy with this drug. A twice-weekly schedule, which is much more effective in rodents and humans, allows much higher doses to be delivered for longer durations, because this schedule is associated with less toxicity. The dose intensity of the twice-weekly schedule, therefore, is much greater than that of the daily oral schedule, if the calculation is based on mg/m²/wk of delivered drug. In practice, the impact of scheduling on the calculation of dose intensity can be

neutralized by comparing programs in which drugs with toxicities affected by scheduling, such as the antimetabolites, are given on similar schedules.

Calculation of an average RDI of a drug combination also assumes that each drug has an equal efficacy against the tumor in question. However, the impact of any single drug or combinations of two or three drugs in a multidrug combination can be assessed separately. This measurement has been done by Hryniuk and colleagues to show the greater impact of cisplatin in a drug combination for ovarian cancer[94–98] and by others[99–102] to show the importance of adequate doses of alkylating agents and vinca alkaloids in lymphoma treatment. This kind of analysis can help identify the most effective drug in a combination and is important because such data can help avoid adjustments that radically alter the effectiveness of a program. Also, by identifying the most important drugs, protocols can be developed that emphasize the dose intensity of these agents compared with other less effective drugs.[36] Negative alterations in dose intensity of the most effective drug in a combination of drugs has great impact, as illustrated in Table 16–4, which displays the effects of the two-drug combination of L-PAM and the antimetabolite 6-mercaptopurine (6-MP) against the Ridgway osteogenic sarcoma model. In this instance, L-PAM is the more effective drug. The relation of average dose intensity of the two drugs to outcome is erratic, but the relation of the dose intensity of L-PAM to outcome is linear. Decreases in the dose intensity of L-PAM reduce the effect of the combination, even if the dose of 6-MP is increased to compensate for these reductions. In fact, any decrease in the dose intensity of L-PAM below 55% of the optimal single-dose schedule results in a loss of the capacity of this combination to cure animals, regardless of the dose of 6-MP.

TABLE 16–4. Ridgway Osteogenic Sarcoma: Effect of Varying Dose Intensity of More Effective Drug, L-PAM

Relative Dose Intensity				*Observed*	
L-PAM	*6-MP*	*Ratio (L-PAM/6-MP)*	*Average*	*% CR*	*% Cures*
0.82	0.49	1.7	0.66	100	60
0.73	1.3	0.56	1.0	90	50
0.55	1.0	0.55	0.78	90	20
0.55	0.33	1.7	0.44	80	20
0.36	0.67	0.54	0.52	56	0
0.36	0.21	1.7	0.29	30	0
0.27	1.5	0.18	0.89	70	0
0.24	0.44	0.57	0.35	0	0
0.24	0.15	1.6	0.20	0	0
0.18	1.0	0.18	0.59	0	0
0.12	0.67	0.18	0.50	0	0
0.08	0.44	0.18	0.26	0	0

L-PAM, L-phenylalanine mustard; 6-MP, mercaptopurine. Tumors weighed 2–3 g. Varying the dose intensity of L-PAM has a greater impact on outcome than can be overcome by increasing the dose of 6-MP.
(Skipper HE. Booklet No. 4. Birmingham: Southern Research Institute, 1986)

To judge adequately the dosing of a particular protocol, data on total dose of each drug used and cumulative doses of each drug are necessary. Collection of such data is not part of routine practice, and reports are not generally available in the literature. To assess the impact of dosing schedules in practice and in clinical trials, such data should be required before papers are accepted for publication.

A positive relation between dose intensity and response rate has been demonstrated in advanced ovarian, breast, and colon cancers and in the lymphomas.[92,93,95,98,100–102]

Calculations of the impact of dose intensity on outcome are particularly important in estimating the value and exploring some of the pitfalls of adjuvant chemotherapy. The steep dose-response curve for anticancer drugs indicates that dose reductions in adjuvant drug treatment programs are likely to be associated with significantly less therapeutic effect. Dose reduction, however, has been the norm in the design of adjuvant trials. An example is the standard CMF regimen for breast cancer referred to in Table 16–3. The model for the regimen was published in 1974 by Canellos and associates.[100] It produced an impressive complete remission rate of approximately 30%, but its toxicity was considerable. As a result, when it was advanced for use in a cooperative group setting, first for advanced disease[99] and later for adjuvant trials by Bonadonna and colleagues,[101] its doses were arbitrarily reduced without pretesting the impact of such reductions on outcome. In addition, further reduction was made, a priori, for patients older than 60 years of age, with the assumption that such reductions would be required because of age. When the effect of these reductions is related to outcome, there is a strong suggestion of a negative impact.[99,102] In premenopausal women the differences in relapse-free survival at the high and low doses of CMF are statistically significant. The most important point, however, is that the average dose intensity of CMF as used in clinical trials and in the community is probably only half the dose intensity of the original program. These dose reductions exceed the levels that animal models predict would lead to a loss in the capacity to cure.

Another example of the potential impact dose intensity can have on the design of clinical trials has been provided by Hryniuk, as shown in Figure 16–3.[93] The dose intensity of 5-fluorouracil is plotted against the response rate for advanced colorectal cancer in panel A. Points indicated by the asterisks are from a single study in which response was reported for actual delivered doses at three different levels.[103] The steep nature of the dose-response curves should be noted. Panel B of Figure 16–3 plots the same three points from the single study but adds the doses used in four published adjuvant studies.[103–108] The doses in all of these studies are well below the level that most investigators would consider the threshold for producing useful responses in advanced colorectal cancer. The effect of dose intensity on the capacity to cure advanced Hodgkin's disease and diffuse large cell lymphomas is also striking and is described in detail in Chapters 51 and 52.

Increasing the dose intensity can be a useful way to improve the effect of certain drugs or combinations of drugs, but it is not useful in all clinical circumstances. Large tumor burdens tend to shift the dose-response curve to the right. At the low end of the curability curve (*i.e.*, in the presence of the highest tumor burdens), increasing the dose intensity often leads to unacceptable toxicity and may not produce more impressive

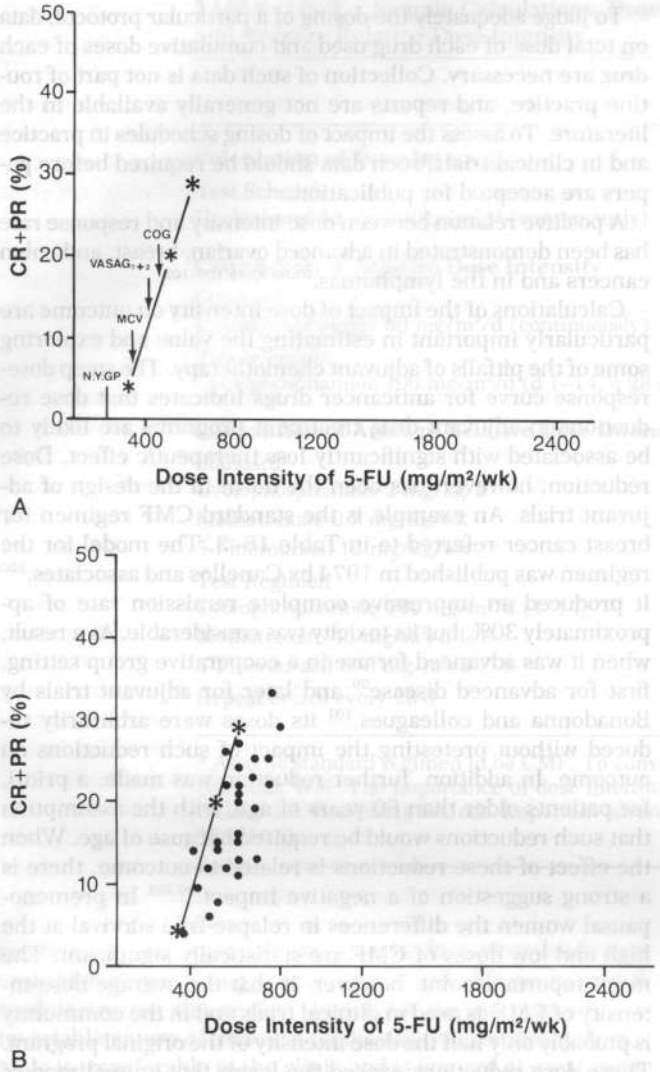

FIGURE 16–3. **(A)** Response rate at various intended dose intensity of 5-fluorouracil in advanced colorectal cancer. Each point represents results from one arm of a randomized trial. *Asterisks* indicate results of three doses from a single study, and *solid circles* indicate received dose intensity. **(B)** Dose intensities of 5-fluorouracil used in four adjuvant studies of colorectal cancer superimposed on the dose-response line for advanced disease shown in panel **A**. *Asterisks* represent received dose intensity from single study (see text). (Hryniuk WM. The importance of dose intensity in the outcome of chemotherapy. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. Important Advances in Oncology 1988. Philadelphia: JB Lippincott, 1988:125)

treatment outcomes, because the dose-response curve is flat. In addition, regimens that are already curing nearly 100% of a subset of patients, such as the combination of platinum, vinblastine, and bleomycin in low-burden testicular cancer and the nitrogen mustard, vincristine, procarbazine, prednisone (MOPP) chemotherapy program in stage IIIA Hodgkin's disease, cannot be expected to be improved on by augmenting dose intensity. However, for most drugs and most tumors, there appears to be a threshold dose that produces responses, and the remarkable success of high-dose chemotherapy programs with bone marrow transplantation support in refractory lymphomas, breast cancer, childhood sarcomas, and neuroblastomas suggests that maximizing dose intensity can improve the chances of cure in drug-responsive tumors.

IN VITRO TESTS TO SELECT CHEMOTHERAPEUTIC AGENTS FOR INDIVIDUALIZED TREATMENT

Short-term assays are not useful in determining the primary treatment for patients for whom a known and effective treatment exists. The assays are also of minimal value for the remainder of newly diagnosed patients and for those with drug-sensitive tumors who fail the first trial of chemotherapy. The basic problem is that the pool of available active drugs is too small for most cancers to make those assays useful beyond clinical judgment. They can, however, be of some use to avoid patient exposure to the toxicity of drugs that are unlikely to be effective, but the tests are too cumbersome and expensive for routine practice. No convincing reports in the literature have indicated that short-term assays provide additional benefit beyond what the clinician can provide by using good judgment and a knowledge of the effectiveness of the limited number of available single agents.

CANCER DRUG DEVELOPMENT

The steps in the development of anticancer drugs are shown in Figure 16–4. The most important step in the drug selection process is mass screening, the mechanism used to narrow the universe of chemicals potentially useful for the treatment of human cancers to a manageable number of high-priority drugs for clinical testing.[105–109] The mass screening effort is conducted by the National Cancer Institute (NCI) drug development program.

Many currently available anticancer drugs active against human leukemias and lymphomas were identified and developed as a result of the NCI system. The input to this type of screening program reached its maximum of 40,000 compounds screened per year in 1975. In 1975, a major change was made in the NCI screening program because of the avail-

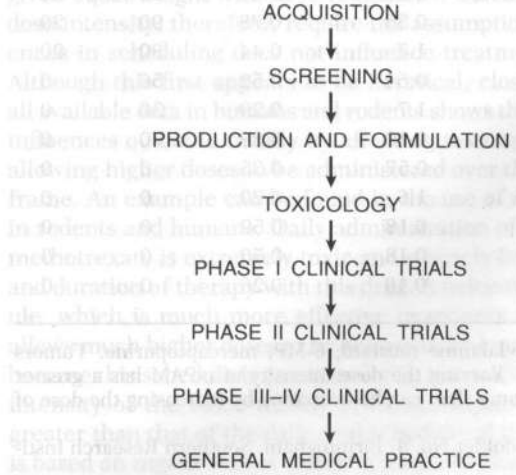

FIGURE 16–4. Steps in cancer drug development.

ability of new rodent models. More rational selection of compounds was coupled with a panel of transplantable rodent tumor screens designed to match the histologic type of common visceral cancers. These rodent solid tumor screens were matched to human tumor cell lines of the same type grown in nude mice. This panel posed the question of the clinical specificity of the preclinical models. The panel of tumors was changed periodically to pose additional questions to the screening process.[110] Taxol, a new agent of considerable interest, was not active in traditional screens but was selected by the new screening panel. Later, human tumors grown in soft agar and under the renal capsule were also introduced into the screening program to further test the hypothesis that the use of human tissue in short-term assays could better select compounds more active in the clinic than could simpler rodent tumor models. Problems with the technical details of these in vitro systems led to their discontinuation.[110–113]

As it became possible to maintain human tumor cells in defined media, the screening program was again changed by developing disease-oriented panels of human tumor cell lines grown in defined media.[113,115] The initial selection of cell lines for this screening panel was based on several considerations, including the use of representatives of major histologic subtypes, the use of multiple cell lines for each tumor type, and the use of cell lines that retain appropriate features of the tumor of origin. The cell lines currently in use include lung, ovarian, and renal cancer; malignant melanoma; brain tumors; and leukemia. Because of the interest in the phenomenon of MDR and the likelihood that it is one of the factors limiting the effectiveness of chemotherapy, a human breast cancer line and an MDR variant of this line, selected for resistance to doxorubicin, are included, along with a murine leukemia and a comparable doxorubicin-induced MDR variant of this murine leukemia. These cell lines provide the potential for identifying new agents with particular activity against MDR cell populations.

A key element in screening strategy is to maintain the capacity for high-volume screening. The most commonly used approach is a colorimetric growth inhibition assay that is based on the metabolic reduction of the tetrazolium salt formazan inside viable cells. Under appropriate conditions, a linear relation is obtained between viable cell number and formazan optical density, measured using a standard enzyme immunosorbent assay plate reader.[116] Automation of this assay has made it possible to maintain an adequate volume of in vitro screening (10,000 compounds per year) at less expense. Preliminary analysis of screening results indicates that individual cell lines show characteristic degrees of in vitro chemosensitivity to individual test compounds with known patterns of clinical activity. Ease of automation of the colorimetric assay and the stability of the cell lines have largely overcome the technical problems associated with clonogenic or subrenal capsular assays.[113,117] The central goal of the in vitro-based, disease-oriented screening program is to identify new antitumor drug candidates that would not have been discovered by the previously available screening program. Clinical testing of these new leads, as with previous versions of preclinical screening, will ultimately be the only way to establish or disprove the validity of the new screen for identifying new drugs active against the common refractory human solid tumors.

In the early days of screening, the acquisition of agents was purely random. Random acquisition of chemicals for screening was associated with two major problems: repetitious screening of compounds already tested and screening of analogs of drugs already known to be active rather than the identification of new structures. Modern molecular biology techniques present an unusual opportunity to select materials, defined at the molecular level, that might prove useful in the inhibition of vital cell functions.

Inherent in all screening systems is the tenet that biologic activity in some preclinical system must be demonstrated before human testing is performed. No currently marketed, useful chemotherapeutic agent is devoid of such preclinical antitumor effect.

Toxicology testing has evolved during the last decade from complicated testing in rodents, dogs, and monkeys to a less expensive and simpler system that relies on toxicity testing primarily in mice. Large amounts of data accumulated since the beginning of anticancer drug development have allowed comparisons to be made across species with respect to common toxicity of chemicals. These data have shown that there is no safety advantage in using larger animal species instead of rodents. In the current system, implemented in 1980, the dose-response curve of a new drug is first developed in mice. The lethal dose (LD) in 10% of animals is determined, and the reproducible lethal dose in 10% of tested animals (LD_{10}) is used as the basis for establishing the initial dose in clinical trials. Usually, 10% of the LD_{10} dose in rodents is selected for the initial human dose; this dose is first tested for toxicity in dogs, before use in humans, to minimize the risks associated with administering an unknown compound to humans. Although the correlation of toxic effects on rapidly dividing normal tissue between rodents, dogs, monkeys, and humans is good, correlation of other toxic effects is not as consistent.[118] Therefore, routine pathologic examination of rodent tissue is not always performed before clinical testing.

All drugs should be given with reference to body weight or surface area. The preferable reference point is body surface area, because better cross-species comparisons can be made, and because calculations based on body surface area allow doses to be determined for adults and children without further

TABLE 16–5. Representative Surface Area to Weight Ratios (km) of Various Species*

Species	*Body Weight (kg)*	*Surface Area*	*Surface Area to Weight Ratio (km)*
Mouse	0.02	0.0066	3.0
Rat	0.15	0.025	5.9
Monkey	3	0.24	12
Dog	8	0.40	20
Human			
Child	20	0.80	25
Adult	60	1.6	37

* To express a mg/kg dose in any given species as the equivalent mg/m^2 dose, multiply the dose by the appropriate *km*. In the adult human, for example, 100 mg/kg is equivalent to 100 mg/kg × 37 kg/m^2 = 3700 mg/m^2.

TABLE 16–6. Equivalent Surface Area Dosage Conversion Factors*

	Mouse, 20 g	*Rat, 150 g*	*Monkey, 3 kg*	*Dog, 8 kg*	*Human, 60 kg*
Mouse	1	$\frac{1}{2}$	$\frac{1}{4}$	$\frac{1}{6}$	$\frac{1}{12}$
Rat	2	1	$\frac{1}{2}$	$\frac{1}{4}$	$\frac{1}{7}$
Monkey	4	2	1	$\frac{3}{5}$	$\frac{1}{3}$
Dog	6	4	$\frac{5}{3}$	1	$\frac{1}{2}$
Human	12	7	3	2	1

* This table shows approximate factors for converting doses expressed in terms of mg/kg from one species to an equivalent *surface area* dose expressed in the same terms mg/kg in the other species. For example, given a dose of 50 mg/kg in the mouse, what is the appropriate dose in the human, assuming equivalency on the basis of mg/m^2?

$$50 \text{ mg/kg} \times \tfrac{1}{12} = 4.1 \text{ mg/kg}$$

adjustment. The assumptions leading to the dose conversion factors have been described in detail by Freireich and coworkers[48] and are shown in Table 16–5, which is useful in converting doses in milligram per kilogram to the comparable milligram per square meter dose. Table 16–6 shows the procedure for conversion of a milligram per kilogram dose in rodents, monkeys, or dogs to the equivalent dose in humans.

EARLY CLINICAL TRIALS OF ANTITUMOR AGENTS

Antitumor agents pass through four phases of clinical testing before they are accepted for general medical practice, marketed, or discarded (see Fig. 16–4).[119–123] The average time from discovery of an effective antitumor agent to marketing of that agent is quite long, in the range of 10 to 12 years, and is expensive, costing $40 million to $80 million.

Although the main purpose of phase I trials is to identify a maximally tolerated dose (MTD) in one of several schedules suggested by the preclinical data, patients are entered into phase I trials with therapeutic intent. For most of the effective anticancer drugs, some therapeutic effect was often seen even in phase I trials. Because a limited number of patients with a variety of diseases are treated in phase I trials, and because doses may be less than the ultimate therapeutic range in a fraction of the patients, the absence of any positive effect in a phase I trial is not a sufficient reason to discontinue testing of a drug. The only reason not to proceed to a phase II study is prohibitive toxicity in phase I trials. Escalation of doses in phase I trials is usually done by a modified Fibonacci system: Doses are first doubled and then increased at decreasing increments of 66%, 50%, and 33% in succeeding groups of patients (usually three at a time) until limiting toxicity is observed.[119] Attempts have been made to rationalize and accelerate dose escalation by the systematic use of preclinical pharmacologic data.[124] This approach has relied on the assumption that the elimination rate of a drug determines its time concentration curve (C ×T), and it further assumes that for agents showing no major differences in target cell sensitivity, schedule dependence, or toxicity between mice and humans, the C × T at the mouse LD_{10} and the human MTD should be similar. These assumptions lead naturally to a simple algorithm for escalating doses by targeting the human C × T in a phase I trial to the mouse C × T at LD_{10}.[121] The steps are as follows:

1. Determine the mouse LD_{10} (part of the routine preclinical toxicology testing discussed earlier).
2. Determine the mouse C × T at LD_{10}.
3. Begin human testing at a safe starting dose (currently one tenth of the mouse-equivalent LD_{10}).
4. Determine the human C × T at the starting dose in phase I.
5. Escalate doses in subsequent patients based on how close the C × T at the starting dose is to the target C × T.

Preliminary studies have suggested that applying this procedure may save 20% to 50% of the escalation steps for many agents. This approach is now being tested prospectively in the NCI phase I testing program.

The definition of a dose as maximally tolerated depends on how much toxicity the patient and physician are willing and able to tolerate. It has been amply demonstrated that for several drugs, such as cyclophosphamide, thiotepa, 1,3-bis(2-chlorethyl)-1-nitrosourea, and etoposide, the MTD, as determined from toxic effects other than bone marrow suppression, is three to ten times higher than the conventional MTD determined by granulocytopenia. The fact that the response rates are commonly a function of dose gives a strong impetus to further trials exploring the upper end of the dose-response curve. As a result, an alternative approach to phase I testing is under consideration, that is, to redefine the MTD as the dose at which unacceptable non-marrow-related toxicity supervenes, despite deployment of all the modern aspects of care. This approach should be greatly facilitated by the availability of colony-stimulating factors, if they succeed in eliminating bone marrow suppression as the rate-limiting step in early testing. It seems prudent to delay decisions on escalation of new agents past the conventionally determined MTD until more information about their clinical characteristics is available.

The purpose of phase II studies is to develop estimates of the response rate to a particular drug of patients with specified tumor types. Phase II studies determine activity rather than clinical usefulness and answer a biologic and clinical question. The outcome of the phase II trial is a decisive point in the development of a drug. These results determine whether a new treatment should be pursued.

When a drug enters phase II testing in individual diseases, it should be tested in a patient group with easily evaluated endpoints of responsiveness, provided it is ethically permissible to do so. This ambition is best fulfilled by enrolling patients with advanced cancer, but who have a maximal performance status, a minimal heterogeneity of metastatic sites, and a minimal amount of prior chemotherapy.[125] This means that for tumors sensitive to chemotherapy, patients who have failed no more than one prior regimen are ideal for study. For the less sensitive epithelial cancers, in many instances previously untreated patients can and should be entered into phase II studies. In view of the poor record of most single agents in heavily pretreated patients with advanced disease, such a strategy seems sensible, because for patients with advanced

drug-resistant cancer, the likelihood of toxicity is much greater than is the likelihood of therapeutic benefit.

The number of patients accrued to phase II trials should be appropriate for the scientific goals of the study. In ideal circumstances, a drug that produces no antitumor effect in 14 patients with the same tumor type, particularly if the heterogeneity of the distribution of metastases is minimized, has a greater than 95% chance of being ineffective against that tumor and could reasonably be eliminated from further studies against that specific cancer. One or two responses, however, increase the chance of efficacy sufficiently to dictate an expansion of the trial to 30 or more patients, so as not to miss a drug with a response rate in the 20% range. In general, partial response rates higher than 20% place the agent in a category of potential clinical usefulness to be determined in further studies. Response rates in the range of 5% to 10% are consistent with observer variation in phase II trials. Response rates lower than than 20% can be meaningful, however, if the quality of the response is good. For example, a few complete remissions, even if the overall frequency of complete response is low, should lead to a decision to proceed with further testing in that disease, because complete disappearance of disease, however infrequent, is an important sign of a potentially effective new treatment. Because multiple doses and schedules may be tested, a phase II trial for each drug, schedule, and tumor type is required before a drug can be disqualified from further clinical use. Given all these confounding variables, a complete phase II trial often requires 600 or more patients.

At the completion of a phase II trial, a decision is made to proceed with or discard the agent. This decision is based on a lack of efficacy or an excessive or intolerable toxicity, against the background of the observed therapeutic effect. Because it is not possible to test each new agent against every tumor type, the potential for discarding agents that might be useful in rare tumors is significant. The early testing results of cisplatin are particularly instructive and illustrative of the problems faced by industry in cancer drug development. Cisplatin showed little activity against the common tumors in its early testing, because it was tested in heavily pretreated patients. Because its use was associated with considerable toxicity, it was almost discarded. Incidental testing in patients with testicular cancer, who are not generally part of major phase II studies, however, revealed interesting activity, and cisplatin was quickly advanced to use in combination with other drugs to treat advanced testicular cancer with curative intent. It was proposed for marketing on the basis of its usefulness in testicular cancer, but few data on its single-agent activity in this disease were available to the Food and Drug Administration in its appraisal of the new drug application, and marketing was delayed almost 3 years, despite nearly uniform enthusiasm for the drug in the oncology community. Only subsequent to widespread aftermarketing testing of cisplatin in other tumors did its broader effectiveness become apparent. This drug has now proved to be not only the mainstay of curative treatment of advanced testicular cancer but an important part of the therapy in lung and bladder cancer, head and neck cancer, ovarian cancer, and other common tumors. The U.S. Government recognized its role in delaying the marketing of this important drug by extending its patent life by 3 years.

If a drug is found effective in phase II trials, phases III and IV testing establishes its place in the therapeutic armamentarium. These clinical trials usually require large numbers of patients and are difficult to perform. The issue of randomized versus historical controls in phases III and IV trials is an important one and is discussed in detail in Chapter 19.

OVERCOMING THE LIMITATIONS OF CANCER TREATMENT

Since it has become apparent that chemotherapy could cure advanced cancers of some types, the question of why it could not cure more cancers, particularly those of the more common histologic types, has plagued investigators. In general, the limitations of cancer treatment have been difficult to overcome until the recent migration of molecular biology methodology to the clinic. The major limitations of cancer treatment are (1) the inability to determine precisely which cancers have metastasized at the time of diagnosis, (2) the inability to detect minimal residual disease after apparently successful treatment, (3) the inability to escalate doses of effective anticancer drugs to the high end of the dose-response curve, (4) the hurdle presented by the unexpected expression of MDR, and (5) the inability to measure the moment-to-moment impact of treatment on cancer cells.

The issue of determining which cancers have metastasized has been addressed indirectly by using panels of prognostic factors, which has proven too crude for practical use in most cancers. It is now being addressed on the molecular level by probing for expression of genes that normally control cell migration; this subject is reviewed in Chapter 8. Molecular diagnosis has advanced to the stage in which the ability to detect minimal residual disease has improved from crude morphologic methods and other tests that detect approximately 1 cancer cell in 20 or 100 normal cells to the ability to detect one malignant cell in 1 million normal cells, using tests such as the polymerase chain reaction. These approaches are reviewed in Chapter 6. We are now in the age in which the availability of colony-stimulating factors (see Chap. 62, section 2) and autologous bone marrow transplantation (see Chap. 62, section 1) are effectively allowing significant dose escalation, and the problems presented by the expression of MDR are in focus and attackable at the clinical level (see Chap. 69, section 6). Although scientists and practitioners are not yet able, at the clinical level, to monitor the impact of cancer treatment on cancer cells moment by moment, techniques such as magnetic resonance spectroscopy and positron emission tomography are available that offer promise. The capacity to measure instantaneously the impact of treatment should radically alter schedules of drug administration to whatever is required to kill cancer cells and no more.

Chemotherapy can cure about 15% of patients with advanced cancers, many of which occur in young patients. The impact of these successes, measured in person-years of life saved, is, however, disproportionately great because the younger average age at diagnosis results in a highly significant salvage of person-years of productive life. Systemic treatment also bears a special burden, because of fear of toxicity in the minds of physicians and patients, beyond that associated with surgery or radiation therapy, and because the effects of systemic therapy cannot be limited precisely to the region in-

TABLE 16–7. Evolution of Cancer Treatment*

RSR (%)	*Date*	*Surgery*	*Radiation Therapy*	*Systemic Therapy*
(±0)	1894	Radical mastectomy	X-Rays discovered	
20	1920	Antibiotics	250 kv units	Transplantable rodent tumors
	1946	Supportive care		Nitrogen mustard in lymphomas
	1955	Radical surgery		Choriocarcinoma
33	1957	Micrometastases	Cobalt units	
	1961		Linear accelerator	Drug cures of leukemia and advanced Hodgkin's disease
36	1970	Resection of metastases	Radiosensitizers	Adjuvant therapy
				Immunotherapy
				Hybridoma technology
	—		Particle therapy	MDR
41	1980	Conservative surgery	Neutron generators	Biologics
		Reconstructive surgery	Treatment planning with CT scans	MoABS
				Dose intensity
				ABMT
49	1985	Tailoring procedures to other treatments	Hyperthermia	Primary chemotherapy
				Overcoming drug resistance
	—		Conformal RRx	Biochemotherapy
	1990	Detect capacity to metastasize		Attacking the signaling system
				Antisense compounds
				Monitor response to treatment
				Determine residual disease

* Illustrates the complexity of integrating advances in each field over a long time span. RSR, relative survival rates from NCI Surveillance, Epidemiology, and End Results (SEER) Program; MDR, multidrug resistance; CT, computed tomography; ABMT, autologous bone marrow transplant; RRx, radiation therapy; MoABS, monoclonal antibodies (also see chapters on principles of surgical oncology [14], radiation therapy [15], and biologic therapy [17]).

volved by tumor. Even though more sophisticated techniques of delivering systemic therapy to target organs have been developed, systemic toxicity is always a concomitant of systemic treatment. The same is true of biologicals. The promise of diminished side effects with the use of biological materials because they were natural products has not been fulfilled. A general principle is that all chemicals, natural or xenobiotic, when used in pharmacologic doses, produce significant side effects.

Patients cured of cancer by any modality generally find the toxicity associated with the treatment a justifiable experience. For those patients with advanced unresponsive cancers, however, who have the burden of progressive tumor and impending death, the risks and side effects of treatment should be carefully balanced against the potential benefits. Patients who are offered systemic therapy with a potential for cure should be treated aggressively; those for whom palliation is the only choice should not be overly burdened with extremely toxic treatments that may prolong life minimally and in an uncomfortable fashion. In practice, this means that patients with metastatic cancer for which no known effective systemic treatment exists often are best advised to avoid treatment with standard anticancer drugs or to take part in one of the many clinical trials testing new treatments.

To expand the benefits of chemotherapy, more use of anticancer drugs before and after surgery and radiotherapy is required when tumor burden is minimal, kinetic features of cell growth are favorable, and drug resistance is less likely to be present or easier to overcome. Because patients sometimes feel free of tumor after surgery, however, they may be less willing to accept the additional trauma of chemotherapy, unless the benefits are carefully explained and accurately and honestly balanced against the chances of recurrence.

Cancer treatment has progressed considerably, despite the frustrations. Nonetheless, the separation of the specialties remains a significant problem; it is often difficult to integrate newer approaches in each field into the practice of medicine. Each field has grown separately,[4] and yet the solutions to clinical problems require the careful integration of components of each specialty.[36] The evolution of the three approaches to cancer treatment are summarized in Table 16–7, which illustrates the complexity of integrating fields that have evolved slowly over eight decades, a time span that considerably exeeds the lifespan of clinical investigators, the change agents in cancer medicine.

REFERENCES

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2. Hersh SM. Chemical and biological warfare: America's hidden arsenal. New York: Bobbs Merrill, 1968.

6 months in untreated patients and assuming exponential growth, it was initially proposed that the natural history of myeloma might require 20 to 30 years to evolve from a single malignant plasma cell to clinically evident disease.[172] In some instances, this model would predict that myeloma was initiated before conception! However, subsequent studies using measurements of M-component metabolism and more precise mathematical modeling techniques determined that the growth of myeloma followed Gompertzian kinetics and that the subclinical phase of malignant tumor cell proliferation was about 1 to 3 years before clinical diagnosis.[171] A typical myeloma growth curve is depicted in Figure 56–4.

The phase of myeloma after diagnosis can be viewed as a chronic phase, not dissimilar to that in chronic myeloid leukemia. This chronic phase in myeloma may last from 1 to 10 or more years, during which time treatment is usually beneficial. Late in the course of myeloma, the doubling time (as determined from serum M-component levels) may progressively shorten; this may be analogous to the blast crisis phase of chronic myeloid leukemia.[173] Integration of tritiated thymidine-labeling index and tumor-burden studies defined these patients as having high-growth-fraction, high-tumor-burden myeloma.[136] This patient group has a poor prognosis, with rapid myeloma growth and early death.[136,174] Patients whose myelomas have more rapid growth kinetics have a propensity for extramedullary tumor growth, including soft-tissue plasmacytomas and central nervous system (CNS) involvement. In some instances, the neoplasm takes on a less-differentiated morphologic appearance, similar to that of a large cell lymphoma, with a cell surface Ig that usually corresponds with the prior serum Ig.[94,175,176]

In earlier phases of disease, the quantity of M-component synthesis as determined from serum or urine measurements corresponds with the amount of tumor in the body. However, in the terminal phase, the M-component synthesis rate per tumor may decline or qualitatively change as the tumor progresses, suggesting the development of a mutant clone. Some patients who previously had only a serum M-component switch to primarily urinary light chains, reflecting additional biochemical abnormalities in Ig synthesis and assembly.[177]

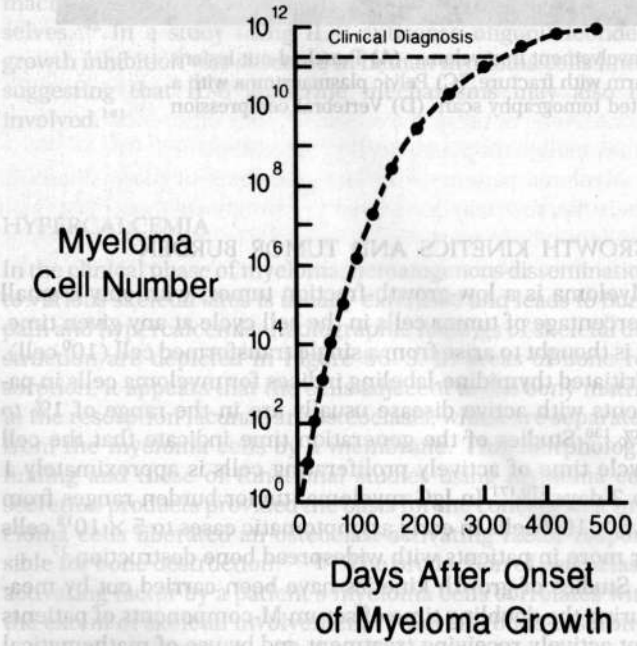

FIGURE 56–4. Gompertzian growth curve in multiple myeloma. In this untreated patient with IgG myeloma, serial measurements of M-component production were used to extrapolate the preclinical phase of myeloma cell proliferation of approximately 1 year.

Unlike the aggressive forms of the disease, another subset of patients have indolent or smoldering myeloma in which, despite evidence of bone lesions, the disease progresses slowly even without treatment. These patients previously could be identified only from their clinical course; however, the use of tritiated thymidine-labeling studies usually identifies these patients as having hypoproliferative myeloma cells, with fewer than 0.5% of the tumor cells labeling and in a range similar to that of MGUS.[135,136]

DIAGNOSIS AND CLINICAL STAGING OF MYELOMA

Presenting symptoms and signs of myeloma usually include bone pain, which may be associated with compression fractures of the spine or pathologic fractures of long bones; weakness and anemia; and infection, usually due to pneumococcal or other gram-positive bacteria. Hypercalcemia, renal failure, spinal cord compression, or a mixture of these findings may be present. Punched-out osteolytic bone lesions are commonly seen on skeletal x-ray films (see Fig. 56–3). A complete skeletal x-ray series, including the axial and appendicular skeleton, should always be obtained at the time of diagnosis. Only in this way can the number and location of lesions be identified to determine if any potentially unstable osteolytic lesions are present.

Studies using magnetic resonance imaging (MRI) scanning suggest that this approach can provide greater detail on myelomatous abnormalities in the vertebral column than conventional radiographs (Fig. 56–5). However, because this procedure is expensive and takes several hours to acquire the imaging information on the entire spine of a single patient, this technique must be used selectively. Bone scans are of no value in the assessment of skeletal involvement in myeloma, because the bone disease is almost purely osteolytic and the nuclear medicine isotopes are taken up only in areas of osteoblastic activity.

An increase in the number of plasma cells is usually demonstrable in the bone marrow or in a biopsy of a plasmacytoma. A serum or urinary M-component can be demonstrated in 99% of the patients. However, in some instances, not all criteria are present, and a mixture of criteria is needed to establish a diagnosis of multiple myeloma and to differentiate it from other plasma cell disorders. Useful diagnostic criteria are summarized in Table 56–3.

A clinical staging system for multiple myeloma was developed at the Arizona Cancer Center by Durie and Salmon by analyzing the presenting features of a series of patients with multiple myeloma who had their tumor burden directly measured using the metabolic techniques.[177] On the basis of these clinical correlations, multiple myeloma was divided into three tumor burden groups: stage I (low), II (intermediate), and III (high). Tumor mass stage alone was predictive of survival.

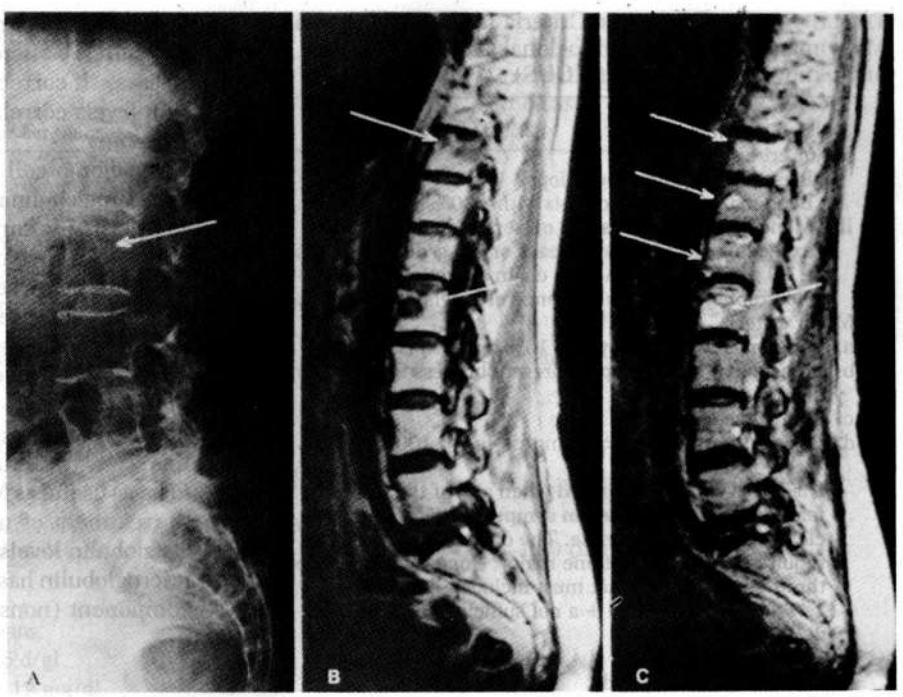

FIGURE 56–5. **(A)** Radiograph of lower spine compared with **(B, C)** magnetic resonance images. The osteolytic lesions in the vertebral bodies of T10–12 and L1 that were poorly visualized on plain films were much more visible on the **(B)** T1-weighted and **(C)** T2-weighted MR images. (Ludwig M, Tscholakoff D, Neuhold A, et al. Magnetic resonance imaging of the spine in multiple melanoma. Lancet 1987;2:364–366)

An additional prognostic factor, renal function, independently impinged on survival and was included in the staging system, with normal renal function (*i.e.*, serum creatinine <2.0 or blood urea nitrogen <30) as substage A and higher values as substage B (Table 56–4).

Several other investigations applied the Durie-Salmon myeloma staging system to evaluate survival by stage in myeloma (Table 56–5). In studies of response to treatment and survival, the clinical features that correlated with a given stage in terms of tumor burden predicted survival in the original patient set and in subsequent reports by other investigative groups.[183,189,190] Figure 56–6 depicts the influence of clinical stage and renal function on the survival of patients with multiple myeloma. In the original study used in developing the Durie-Salmon myeloma staging system, the percentage of bone marrow plasma cells was an important factor, but it was not included in the staging system because it could be replaced by other clinical features and was potentially susceptible to sampling errors. Bone marrow involvement was deleted from the staging criteria after consideration of the potential difficulties that might be encountered in accurately and reproducibly counting plasma cells in the bone marrow differential at different centers. Patients with Bence Jones-only myeloma have been assessed for measured tumor cell burden, and they appear to represent a higher-risk subgroup with a higher tumor cell mass and shorter survival.[192]

DIFFERENTIAL DIAGNOSIS

The criteria shown in Table 56–3 provide the basis for differentiating myeloma from other major plasma cell disorders with M-component secretions other than IgM. The IgM M-components are usually attributable to Waldenström's macroglobulinemia and occasionally to MGUS or other entities. Multiple myeloma with IgM secretion has rarely been reported, and it should be diagnosed only if the patient has multiple osteolytic bone lesions that contain monoclonal plasma cells.[94] Marrow plasmacytosis is observed in several chronic infectious or inflammatory diseases and in hypersensitivity reactions, autoimmune disease, unrelated neoplasms, and occasionally in other conditions; it is not associated with secretion of an M-component, but it is associated with polyclonal hyperglobulinemia.

The major differential diagnosis is usually between myeloma and MGUS. There is an overlap between the findings for patients with MGUS and those with stage I myeloma (or macroglobulinemia) that can often be recognized only by serial follow-up of the patient for at least 1 year without any form of treatment. In MGUS, the M-component level remains constant over many years, but in the malignant plasma cell disorders, the M-component gradually rises, and other symptoms and signs of the disease develop. A policy of watch and wait is completely justifiable, because there is no evidence that treatment improves the outcome in stage I myeloma or MGUS, and the use of chemotherapy has potential hazards that should be avoided if the patient does not have an invasive, progressive plasma cell malignancy. If, after a year's follow-up of the patient's M-component and symptoms and signs at 1- to 2-month intervals, there is no evidence of progression, the most likely diagnosis is MGUS, and follow-up examinations should be done at least annually because approximately 2% of these patients progress to a diagnosis of B-cell neoplasm each year.[1]

Patients presenting with only Bence Jones proteinuria usually have myeloma alone or with amyloidosis.[193,194] It has been stated that its excretion has "sinister significance."[195] However, Bence Jones MGUS has been reported and followed without specific therapy for several years in a few patients.[160,196] It is nonetheless reasonable to have a higher index of suspicion when patients present with idiopathic Bence Jones proteinuria, because it usually progresses within 6 months to 1 year to clearly diagnosed myeloma, which should be treated

TABLE 56–3. Diagnostic Criteria for Multiple Myeloma, Myeloma Variants, and Monoclonal Gammopathy of Unknown Significance (MGUS)

A. Multiple myeloma
   Major criteria
   I. Plasmacytoma on tissue biopsy
   II. Bone marrow plasmacytosis with >30% plasma cells
   III. Monoclonal globulin spike on serum electrophoresis exceeding 3.5 g/dl for G peaks or 2.0 g/dl for A peaks, ≥1.0 g/24 h of κ- or λ-light chain excretion on urine electrophoresis in the presence of amyloidosis
   Minor criteria
   a. Bone marrow plasmacytosis 10% to 30% plasma cells
   b. Monoclonal globulin spike present but less than the level defined above
   c. Lytic bone lesions
   d. Residual normal IgM < 50 mg/dl, IgA < 100 mg/dl, or IgG < 600 mg/dl*
   Diagnosis will be confirmed when any of the following features are documented in symptomatic patients with clearly progressive disease. The diagnosis of myeloma requires a minimum of one major + one minor criterion or three minor criteria that must include a + b, *i.e.:*
   1. I + b, I + c, I + d (I + a not sufficient)
   2. II + b, II + c, II + d
   3. III + a, III + c, III + d
   4. a + b + c, a + b + d
B. Indolent myeloma (same as myeloma except)
   I. No bone lesions or only limited bone lesions (≤3 lytic lesions): no compression fractures
   II. M-component levels: (a) IgG < 7 g/dl; (b) IgA < 5/dl
   III. No symptoms or associated disease features, *i.e.:*
   a. Performance status > 70%
   b. Hemoglobin > 10 g/dl
   c. Serum calcium normal
   d. Serum creatinine < 2.0 mg/dl
   e. No infections
C. Smoldering myeloma (same as indolent myeloma except)
   I. No bone lesions
   II. Bone marrow plasma cells ≤ 30%
D. MGUS
   I. Monoclonal gammopathy
   II. M-component level
   IgG ≤ 3.5 g/dl
   IgA ≤ 2.0 g/dl
   BJ protein ≤ 1.0 g/24 h
   III. Bone marrow plasma cells < 10%
   IV. No bone lesions
   V. No symptoms

* IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; BJ, Bence Jones light chain.
(From references 135, 160, 179, 180)

appropriately. Patients with unrelated metastatic neoplasms occasionally have MGUS, and a series of diagnostic studies and biopsies are required to establish that the patient does not have myeloma. Myeloma and an unrelated metastatic neoplasm may be diagnosed.

β_2-MICROGLOBULIN

β_2-microglobulin is an important prognostic factor in multiple myeloma.[197] It is a low-molecular-mass protein, which is the light chain of the HLA antigen and is synthesized by all nucleated cells.[198] It falls in the class of tubular proteins that pass the glomerulus and are excreted in the urine, but renal functional impairment elevates the serum level of β_2-microglobulin. β_2-Microglobulin can be measured by radioimmunoassay. If corrected for renal function, serum β_2-microglobulin levels correlate strongly with tumor burden in multiple myeloma.[197,199–203] Because the serum levels are a function of myeloma cell mass and renal function, measurement of β_2-microglobulin may provide an alternative to clinical staging for predicting survival.[204] The relation of β_2-microglobulin to survival in myeloma is depicted in Figure 56–7. β_2-Microglobulin can serve as a pretreatment prognostic factor in clinical trials because it permits a more direct comparison of risk factors among the various cooperative groups and institutions interested in myeloma therapy.[205,206] Although it has been proposed that β_2-microglobulin can be used to differentiate between MGUS and myeloma, significant overlap prevents this.[197,200,207] Serial β_2-microglobulin levels have not proven to be as useful as M-component measurements after response to treatment of myeloma. INF-α is reported to raise β_2-microglobulin levels in myeloma.[208] In our own experience, β_2-microglobulin has not proved useful in patients lacking an M-component (nonsecretory myeloma).

TREATMENT

PRINCIPLES

The diagnosis of a monoclonal gammopathy does not represent an immediate mandate for treatment, and patients with MGUS, stage I myeloma, and indolent or smoldering myeloma are often best followed without treatment until it is warranted by the development of clear-cut progression of the disease.

Because multiple myeloma is a disseminated plasma cell neoplasm, the primary approach to treatment is systemic antineoplastic therapy. Symptoms and signs that warrant immediate institution of therapy include the development of bone pain, hypercalcemia, renal failure, severe suppression of bone marrow functions, or spinal cord compression. If the patient has spinal cord compression, completion of local therapy (usually with radiation therapy) should normally precede the initiation of systemic chemotherapy unless other serious complications mandate simultaneous systemic treatment and radiation therapy. Patients presenting with long-bone fractures should have them internally fixed orthopedically before the initiation of chemotherapy. Presentation with constellations of findings, such as marked anemia plus the presence of lytic bone lesions, bacterial sepsis, or Bence Jones proteinuria, provide reasons for initiation of therapy. If there is significant infection, initiation of treatment should usually be delayed until the infection has been controlled. If the clinical findings are ambiguous, a period of observation that includes serial M-component measurements is usually warranted.

Doubling in the M-component in less than 1 year with other clinical findings of myeloma can also be used as a basis for treatment. For example, patients with rising M-component levels or progressive bone lesions are candidates for treatment even if they are asymptomatic. Useful adjuncts to systemic treatment include management of local problems with radiation therapy and a variety of supportive care measures.

Beneficial effects of systemic therapy can be obtained in most patients with newly diagnosed progressive myeloma in

TABLE 56–4. Myeloma Staging System

Criteria	Measured Myeloma Cell Mass (Cells × $10^{12}/m^2$)
Stage I	
All of the following:	
Hemoglobin value > 10 g/dl	
Serum calcium value normal (<12 mg/dl)	
On roentgenogram, normal bone structure (scale 0) or solitary bone plasmacytoma only	
Low M-component production rates	<0.6 (low)
IgG value < 5 g/dl*	
IgA value < 3 g/dl	
Urine light chain M-component on electrophoresis < 4 g/24 h	
Stage II	
Overall data not as minimally abnormal as shown for stage I and no single value as abnormal as defined for stage II.	0.6–1.20 (intermediate)
Stage III	
One or more of the following	
Hemoglobin value < 8.5 d/gl	
Serum calcium value > 12 mg/dl	
Advanced lytic bone lesions (scale 3)	
High M-component production rates	>1.20 (high)
IgG value > 7 d/gl	
IgA value > 5 g/dl	
Urine light chain M-component on electrophoresis > 12 g/24 h	
Subclassification	
A = relatively normal renal function (serum creatinine value > 2.0 mg/dl)	
B = abnormal renal function (serum creatinine value ≥ 2.0 gm/dl)	
Examples	
Stage IA = low cell mass with normal renal function	
Stage IIIB = high cell mass with abnormal renal function	

* IgA, immunoglobulin A; IgG, immunoglobulin G.
(Alexanian R, Balcerzak S, Bonnet JD, et al. Prognostic factors in multiple myeloma. Cancer 1975;36: 1192–1201)

TABLE 56–5. Median Survival in Relation to Stage at Diagnosis

Investigations	No. of Patients	Median Survival (mo)				
		Stage				
		I	II	III	A	B
Durie and Salmon[181]	71	>60	50	26		
Alexanian et al[182]	343	39	27	17		
Woodruff et al[183]	237	64	32	6	21	2
Merlini et al[184]	123	76	41	12		
Belpomme et al[185]	118	>60	28	7	>60	12
Gobbi et al[186]	91	>79	51	33		
Santoro et al[187]	81	48	41	23	35	7
Bergsagel et al[188]	364	46	32	23	32	11
Summary	1428	>60	41	23		

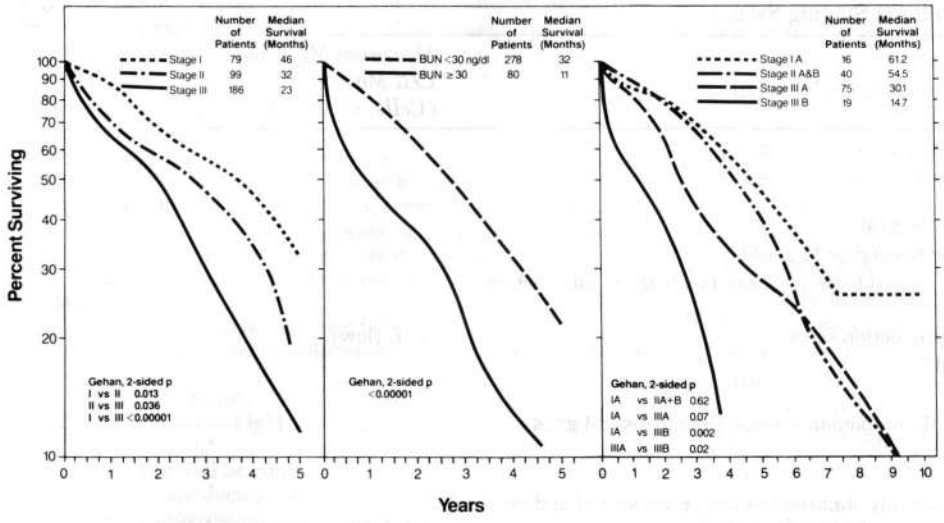

FIGURE 56–6. Influence of clinical stage and renal function on survival of patients with plasma cell myeloma as redrawn from published illustrations. The left two panels are from a Canadian NCI study[189] and show the separate effects of clinical stage and renal function, respectively. The right panel depicts an Arizona Cancer Center study,[191] and the survival curves are shown with clinical stage and renal function integrated with the use of the clinical staging system shown in Table 56-4. Statistical comparisons of survival outcome for the various stages and risk groups in the studies appear in each panel.

clinical stages II or III. The best improvement in survival of patients with myeloma has been obtained for those with stage III disease. The clinical phases of myeloma under treatment include an initial drug sensitive phase, which is observed in most patients; a plateau phase, during which tumor burden is reduced and appears to be stable during maintained or unmaintained remission; and an eventual drug-resistant phase, during which the neoplasm may exhibit altered growth kinetics and resistance to conventional cytotoxic drugs.[2,209] About 15% to 20% of patients manifest resistance even to aggressive parenteral chemotherapy at the time of initial presentation with progressive myeloma.

Systemic therapy usually relieves bone pain relatively promptly, but many other aspects of the disease improve gradually and may require other supportive measures initially. Even with prompt institution of systemic treatment, the drug-sensitive phase of disease usually lasts only 2 to 3 years for most patients before drug resistance manifests. Although the median survival before the era of effective systemic therapy was less than 1 year, it is now in the range of 3 to 4 years. In a few patients, sensitivity to systemic therapy may persist for 5 to 10 years or longer.

Care must include maximal efforts to relieve pain, hypercalcemia, severe anemia, and various local complications promptly to keep the patient from being bedridden, minimizing bone demineralization and superinfections. Patients should be encouraged to drink several liters of fluid daily to avoid dehydration and enhance urinary excretion of light chains and calcium.

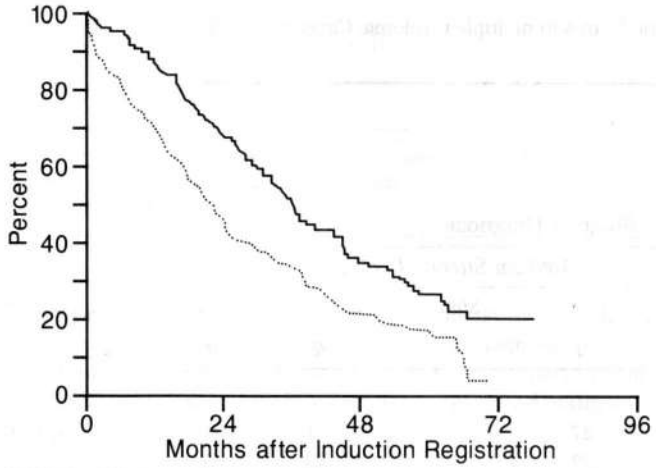

FIGURE 56–7. Life table survival curves in multiple myeloma in relation to serum β_2-microglobulin (β_2M) concentration. The upper curve (*solid line*) is for 324 patients with a serum concentration of less than 6 g/ml (median survival, 36 months). The lower curve (*dotted line*) is for 224 patients with higher serum levels (median survival, 22 months; $p < 0.0001$). (Salmon SE, Tesh D, Crowley J, et al. Chemotherapy is superior to sequential hemibody irradiation for remission consolidation in multiple myeloma: A Southwest Oncology study. J Clin Oncol 1990;8:1575–1584)

EVALUATION OF RESPONSE TO TREATMENT

Because myeloma has a variety of clinical manifestations, a series of initial and follow-up studies are needed to assess the response to systemic treatment. These include a thorough history, physical examination, and following laboratory studies, which include the complete blood count with differential and platelet counts; M-component levels in the serum, 24-hour urine, or both; serum calcium, creatinine, or blood urea nitrogen levels; and skeletal radiographs. Although serum electrophoresis is extremely useful in the initial diagnostic workup, baseline and follow-up quantitation of the serum M-components is most reliably measured using laser nephelometry of the involved immunoglobulin. Serum electrophoresis is sometimes a useful alternative, particularly as the M-component level approaches the normal range for the involved Ig. The radial immunodiffusion test should not be used to measure myeloma immunoglobulins, because it has not proved reliable. Quantitation of urinary Bence Jones protein is best determined by protein electrophoresis using a 24-hour concentrate. The relative value of β_2-microglobulin useful for following the course of myeloma has not been established, but β_2-microglobulin is not as specific as M-component measurements, because its serum concentration is affected by tumor burden and renal function.

In the absence of specific symptoms, follow-up radiographs should be obtained every 6 to 12 months. The initial skeletal

x-ray evaluation before therapy should include a complete metastatic survey, because myelomatous involvement can be located in any area of the axial or appendicular skeleton. Isotopic bone scans are of little or no value for myeloma and are not recommended. Bone marrow involvement should be assessed initially with an aspirate and a core bone marrow biopsy. Caution is needed to avoid excessive pressure on the needle when the needle is inserted, because in some myeloma patients, the bone matrix is extremely fragile. Follow-up bone marrow specimens are obtained to confirm remission status after therapy and to explain an unexpected pancytopenia. Marrow involvement with myeloma is usually diffuse, but occasionally it is spotty and may be subject to sampling error for needle aspiration but usually not for core biopsy. "Dry taps" on aspirates can be due to needle placement within a plasmacytoma. Table 56–6 summarizes a useful schedule for obtaining initial and follow-up studies in myeloma patients.

M-component production usually correlates with tumor burden in myeloma patients, and its serial assessment usually provides an excellent guide to the response to treatment or disease progression. Objective response criteria should identify patients who have achieved significant tumor regression and separate them from patients who have only stabilized or who have had symptomatic improvement without having achieved remission status. In 1973, the Leukemia-Myeloma Task Force of the NCI published the criteria for response in myeloma, which required a 50% reduction in the serum or urinary levels of an M-component to define remission.[210] Although the task force criteria were created to identify groups of patients responsive to treatment, they were developed before the acquisition of detailed knowledge of Ig metabolism. Analysis of Ig metabolism led to the recognition that for the major classes of IgG (IgG1, IgG2, and IgG4, which comprise 90% of serum IgG), metabolism is not linear with the serum concentration.[211] With a relatively high serum IgG M-component value, the half-life of IgG may be as short as 8 to 10 days, but with a low value, the half-life may be 40 days or longer. This concentration-dependent phenomenon applies to IgG M-component levels in 90% of patients with IgG myeloma or approximately 50% of all myeloma cases. Comparisons of serum levels in these patients underestimate the degree of change, depending on the initial and follow-up serum M-protein values.[2] Correction can be made for changes in the metabolic rate for IgG through the calculation of a synthetic index from the serum values.[212] A useful nomogram for this purpose has been derived from the metabolic equations.[2] A nomogram with an extended scale for IgG values appears in Figure 56–8.

Assessment of urinary light chain excretion is affected significantly by the degree of catabolism that takes place in the kidney, which is a function of the absolute levels of light chains passing the glomerulus and the degree of renal functional impairment.[192] To avoid difficulties in assessment, criteria for improvement in Bence Jones proteinuria must be quite stringent. The response criteria adopted by SWOG are summarized in Table 56–7. Response in accord with the SWOG criteria is strongly correlated with improvement in survival. When these criteria are applied, reduction in the synthetic index of serum M-proteins to less than 10% of control levels is associated with a better survival than if reduction is 10% to 24%, which is better than a reduction to 24% to 50% of control values. Lesser degrees of reduction in tumor burden are not associated with improvement in survival. Patients whose hemoglobin, renal function, and albumin levels improve have a better outcome than if the clinical variables remain unchanged or worsen. Responsive patients have improvement in general well-being and in ambulation, and they have marked relief of symptoms of bone pain. However, recalcification of osteolytic bone lesions is observed in fewer than 5% of patients who respond to chemotherapy.

A retrospective analysis of 69 stage II and 80 stage III myeloma patients treated at a single institution was evaluated with Myeloma Task Force and SWOG response criteria.[213] In

TABLE 56–6. Checklist of Laboratory Studies for Patients With Multiple Myeloma

Routine Pretreatment Evaluation
Complete blood count, differential, and platelets
Serum protein electrophoresis
Serum immunoglobulins (nephelometry)
Serum β_2-microglobulin
24-h urine for total protein and electrophoresis
Antigenic typing of serum and urine monoclonal Igs by immunofixation or immunoelectrophoresis
Bone marrow aspiration and biopsy
Serum creatinine
Serum calcium
Serum electrolytes
Serum uric acid
Liver functions
Chest radiograph
Skeletal x-ray survey (entire skeleton)
Electrocardiogram
Specialized Studies for Selected Patients
Abdominal fat pad or rectal biopsy for amyloid (also tap joint effusions for amyloid)
Solitary lytic lesion, soft tissue or lymph node biopsy
Serum viscosity if IgM component present or if any serum M-component > 7.0 g/dl
Plasma volume if serum relative viscosity > 4.0
Myelogram (or in some instances MRI) if paraspinal mass or symptoms and signs of spinal cord or nerve root compression. (Spinal fluid should be sent for cell count, cytospin differential, glucose, and protein.)
Routine Follow-Up Studies
Before every course of treatment
CBC, differential, platelets (should be repeated to check nadirs on first few courses)
At least every 3 months (and on completion of induction or change to alternative therapy for refractory patients)
Serum monoclonal Ig by nephelometry or electrophoresis
24-h urine protein electrophoresis (if Bence Jones protein present)
Serum chemistry panel
At least annually
Skeletal x-ray survey (entire skeleton), chest film, serum β_2-microglobulin
Bone marrow aspiration if any significant abnormality in blood counts, Igs, or new symptoms
Serum Igs (nephelometry)

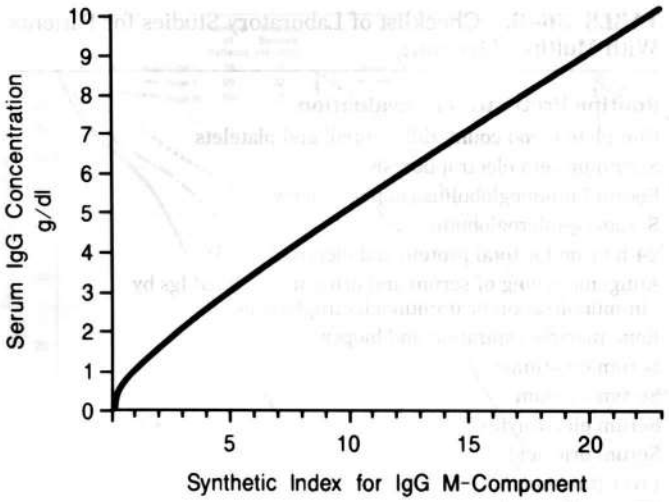

FIGURE 56–8. Nomogram for determining the synthetic index for IgG M-components of subclasses IgG1, IgG2, and IgG4, which comprise 90% of IgG myelomas. Using the patient's initial serum IgG concentration (g/dl) on the vertical axis, read down from the line to the horizontal axis to determine the synthetic index for that IgG value (Syn1). The same procedure is followed for the follow-up value (Syn2). Syn2/Syn1 × 100 = % of baseline synthetic index and tumor burden. This nomogram corrects for concentration-dependent changes in M-component synthesis and myeloma cell mass and gives a more accurate assessment of changes in tumor burden in IgG myeloma than can be calculated directly from the serum levels. The nomogram is not required for IgG3, IgA, IgD, or IgM serum M components, and changes in serum values for these Igs can be used directly to determine the percent change in tumor burden. The equation used to develop this nomogram has been incorporated into a program for a pocket calculator to calculate tumor cell mass. (Salmon SE, Wampler SE. Multiple myeloma: Quantitative staging and assessment of response with a programmable pocket calculator. Blood 1977;49:379–389)

TABLE 56–7. SWOG Myeloma Response Criteria

A. Responsive patients who satisfy all of the following criteria are considered to have achieved definite objective improvement.
   A sustained decrease in the synthesis index of serum M protein to 25%, or less, of the pretreatment value on at least two measurements separated by 4 wk. For IgA and IgG3 M-proteins, the synthetic index is the same as the serum concentration. For IgG M-proteins of subclasses 1, 2, and 4, the synthetic index must be estimated using the nomogram shown in Figure 47-6.
   A sustained decrease in 24-h urine globulin to 10%, or less, of the pretreatment value, and to less than 0.2 g/24 h on at least two occasions separated by 4 wk.
   In all responsive patients the size and number of lytic skull lesions must not increase, and the serum calcium must remain normal. Correction of anemia (hematocrit > 27 vol. %) and hypoalbuminemia (>3.0 g/dl) is required if they are considered to be secondary to myeloma.
   With equivocal data (*e.g.*, nonsecretors, L chain producers for whom the pretreatment urine collection was lost), the following support the conclusion that an objective response has occurred:
      Recalcification of lytic skull lesions.
      Significant increments in depressed normal immunoglobulins (*e.g.*, increments >200 mg/dl IgM, >400 mg/dl IgA, and >4000 mg/dl IgG).
B. Improved patients show a decline in the serum M-protein synthesis rate to less than 50%, but not less than 25% of the pretreatment value.
C. Unresponsive patients fail to satisfy the criteria for responsive or improved patients.

(Alexanian R, Bonnet J, Gehan E, et al. Combination chemotherapy for multiple myeloma. Cancer 1972;30:382–389)

carrying out this analysis, 2 stage II patients and 9 stage III patients who failed to live 3 months were censored to minimize the "guarantee time" inherent in including early deaths as nonresponders by usual statistical methods. The researchers concluded from this analysis of a relatively small series of patients that the Myeloma Task Force criteria of response may have similar predictive value to that of the SWOG for stage II patients. They found that the SWOG criteria had greater predictive value for stage III patients but believed that the latter difference was of questionable significance. Further analysis of significantly larger patient populations is warranted to authenticate the association of M-component reduction and tumor regression in multiple myeloma.

RADIATION THERAPY

Palliation for Bone Pain and Soft Tissue Masses

Radiation therapy has been recognized for many years as a rapid and highly effective palliative agent in the treatment of multiple myeloma.[225–229] Despite advances in the systemic treatment of this disease, radiation therapy continues to be important. It has been estimated that almost 70% of all patients eventually require and potentially benefit from treatment with irradiation.[230]

Treatment of painful, disabling bony sites is usually rapidly successful because of the radioresponsive nature of myeloma. In addition to rapid relief of pain, with accompanying decrease in narcotic requirements, pain relief allows patients to maintain much more normal activity, reducing the structural weakness in bone caused by calcium loss from bedrest. Because treatment is often rapidly effective at relatively modest doses, irradiation can arrest local tumor progression in bone and prevent pathologic fractures, minimizing the morbidity of more invasive therapeutic interventions for these patients. These positive features of irradiation enable a much more normal functional existence for patients.[225–228]

Myeloma is usually quite responsive to radiation therapy, and tumor doses of approximately 2000 to 2400 cGy in five to seven fractions over 1 to 1.5 weeks are usually sufficient.[226,228] Relief of pain is obtained in more than 90% of treated patients.[230,231] From 30% to 65% of responses are complete.[230] An analysis of 100 patients treated at the University of Arizona demonstrated no increase in response probability with doses greater than 1500 cGy. Limited numbers of sites were treated with lower doses. Neither the probability of recurrent symptoms nor the time to relapse at the treated site was influenced by the radiation dose. Except for solitary disease, higher doses have not been advantageous, and because of the generalized nature of the disease and its relatively long natural history, higher doses may preclude a necessary second course of treatment to a site caused by tumor reseeding, extension, or regrowth.

Careful treatment planning is necessary to ensure inclusion

of the entire lesion(s) responsible to the localized problem, and imaging studies such as computed tomography (CT) scans may be helpful in delineating the extent of tumor.

Judgment and experience are necessary in determining when radiation therapy is appropriate (versus systemic treatment), especially early in the course of this often chronic condition. Although irradiation relieves the most disabling symptom(s), a similar result often can be achieved by chemotherapy, especially early in the course of myeloma, with no resultant compromise in future delivery of chemotherapy because of myelosuppression. This is particularly true in the treatment of sites containing considerable bone marrow, such as the pelvis. A Cancer and Leukemia Group B (CALGB) study that attempted "total bone marrow" treatment by sequential irradiation in combination with chemotherapy was not beneficial.[232] Recirculation of myeloma into previously treated sites may partially explain the negative study.[233] Ideal management requires close coordination with the physician administering the patient's systemic chemotherapy.

Structural changes brought about by tumor involvement may, by nerve compression or orthopedic instability, be responsible for a substantial portion of a patient's pain. It is usually a mistake to treat a patient with multiple myeloma to progressively higher doses than those previously used if some level of pain persists, assuming that careful prior imaging studies and treatment planning have been accomplished.

Special Indications for Radiation Therapy

Several other localized manifestations of myeloma may be indications for palliative irradiation, especially in the patient who has proved resistant to most conventional systemic agents. Included are patients who present with proptosis caused by sphenoid or orbital bone involvement, those who present with dental or facial abnormalities caused by maxillary or mandibular involvement, or those who present with CNS symptoms caused by extensive calvarial or base of the skull involvement. A treatment philosophy and approach similar to that for palliation of bone pain is appropriate.

CHEMOTHERAPY

Systemic Chemotherapy

The initial approach to treatment for most patients with symptoms and signs of progressive disease is with systemic chemotherapy. Cycle-nonspecific cytotoxic drugs, particularly alkylating agents, represent the current mainstay of standard therapy.

Bifunctional alkylating agents, particularly melphalan and cyclophosphamide; nitrosoureas, including carmustine and lomustine (CCNU); doxorubicin; and glucocorticoids represent the major active agents used in systemic therapy for multiple myeloma.[23,26,27,214,215] Vincristine has been used in several treatment programs; although there is evidence it can reduce tumor burden somewhat, there is no indication that its addition to other drugs increases survival.[216–218] INF-α has antitumor activity in myeloma and is currently under investigation to determine whether it can play a role with other systemic agents in the drug-sensitive phase of disease.[219–224] All of these agents have been subjected to clinical trials as single agents in myeloma and have been incorporated into various drug combinations for evaluation in previously untreated patients.

Remission-Induction Chemotherapy

ALKYLATING AGENTS WITH OR WITHOUT PREDNISONE. A variety of simple alkylating agent—prednisone combinations and more complex regimens have been used for remission induction for patients with multiple myeloma. Overall objective response rates in various series using single alkylating agents alone or in combination with prednisone usually are 20% to 70%, and the rates are influenced by the response criteria used and the aggressiveness with which the regimens can be administered because of their myelosuppressive effects. Prednisone and other glucocorticoids have been combined with alkylating agents because of their single-agent activity, lack of overlapping toxicity, and the suggestion that they may potentiate the action of other agents. In most instances, patients in these trials received maintenance chemotherapy after remission induction.

Many studies used a variety of schedules of oral administration of melphalan or cyclophosphamide alone or in combination with prednisone, with generally similar therapeutic results. Useful dosage schedules for the commonly used alkylating agents appear in Table 56–8. Dosage adjustments for myelosuppression are commonly employed, but dose escalation in the absence of myelosuppression is not usually followed satisfactorily. Inadequate dose escalation (particularly with melphalan) can produce significant underdosing. Melphalan has variable absorption by the oral route, and the drug is best absorbed when ingested on an empty stomach.[234] Although oral absorption is not usually a problem with oral cyclophosphamide or CCNU, regular monitoring of the leukocyte count and differential count can detect patients with compliance problems with the self-administration of oral agents. Nadir absolute granulocyte counts below 2000/μl should be achieved between intermittent courses of therapy, but with continuous courses, the dosage should be adjusted to

TABLE 56–8. Selected Schedules Using Intermittent or Continuous Schedules of Alkylating Agents for Treatment of Myeloma Alone or in Combination With Prednisone

Intermittent Schedules	
Cyclophosphamide	
I.V.	1000 mg/m^2 (27 mg/kg) q 3 weeks (Significantly higher doses now being evaluated)
Oral	250 mg/m^2 per d × 4d q 3 wk
Melphalan	
I.V.	16 mg/m^2 q 2 wk × 4 then q 4 wk Reduce initial dosing by 50% if serum creatinine > 2.0 mg/dl (BUN > 30 mg/dl)
Oral	8 mg/m^2 q 3 wk or 9 mg/m^2 q 4 wk (Because of varying bioavailability of oral melphalan, the dose must be increased to induce hematologic toxicity or significant underdosing may occur.)
Carmustine (BCNU)	
I.V.	100–150 mg/m^2 q 4–6 wk
Lomustine (CCNU)	
Oral	130 mg/m^2 q 4–6 wk

maintain the leukocyte count between 2000 and 3500/μl. Although intravenous schedules provide more predictable dose delivery, the largest experience has been with oral regimens.

Regardless of the dosage schedules or objective response rates in major clinical trials, the median survival time of patients receiving oral melphalan or cyclophosphamide alone or in combination with prednisone have ranged from 18 to 35 months, with an overall median of about 24 months (Table 56–9). Some "response rates" have varied because different criteria were used to determine objective response in the reported studies. Similar results have been observed with the nitrosoureas, although these agents have not been studied extensively.[26]

The survival outcome in myeloma patients is now clearly superior to that observed before the introduction of alkylating agents, when median survival times from diagnosis were in the range of 3.5 to 11.5 months.[235–237] The improvement in survival that occurred in myeloma after the introduction of the alkylating agents is due to these drugs, rather than to changes in earlier diagnosis or changes in supportive care. Equivalent therapeutic effects have been reported with intermittent and continuous schedules. An initial loading dose followed by a subsequent continuous dose, as used by the CALGB, produced similar results.[25] Intermittent schedules may have advantages in terms of assuring regular monitoring of the patient's progress and avoiding cumulative toxicity.

MULTIAGENT COMBINATION CHEMOTHERAPY. An area of continuing controversy for myeloma therapy is the comparative effectiveness of the simple oral melphalan plus prednisone (MP) or cyclophosphamide plus prednisone (CP) combinations with more complex regimens. Several institutions and cooperative groups have explored a variety of multiagent combinations, with a subset of these studies reporting significantly better survival results than have been observed with the simple combinations; however, this is far from uniform. Multiagent combinations incorporate agents with different mechanisms of action, little or no cross-resistance, and reduced overlapping toxicities, enabling greater cytoreduction of the myeloma cell burden. Some experimental evidence suggests that combinations of alkylating agents may be potentiating because there are different mechanisms of membrane uptake and other potential differences in their mode of action and cellular cytotoxicity.[245]

Some of the most widely used multiagent combinations include the M2 protocol developed at Memorial Sloan-Kettering Cancer Center[246] and the alternating combination chemotherapy regimens developed by SWOG.[190] In the initial SWOG report of alternating combinations, vincristine, melphalan, carmustine, and prednisone (VMCP) was alternated with vincristine, carmustine, doxorubicin, and prednisone (VBAP) or vincristine, cyclophosphamide, doxorubicin, and prednisone (VCAP).[190] In subsequent trials, the alternation has been limited to VMCP and VBAP, because VBAP can reinduce remission in myeloma patients who have previously responded and relapsed from therapy with melphalan or cyclophosphamide combinations.[247] The dosage schedules for these Memorial Sloan-Kettering and SWOG combination programs are summarized in Table 56–10. The fifth Medical Research Council's (MRC5) trial of alternating combination chemotherapy used

TABLE 56–9. Effects of Some Major Trials of Single Alkylating Agents Alone or in Combination With Prednisone on Survival in Multiple Myeloma

Investigations	*Treatment* (Alkylating Agent Scheduled)*	*No. of Patients*	*Response Rate†*	*Median Survival From Start of Therapy (mo)*
Alexanian et al[238]	Melphalan (i)	82	49–59	23
Alexanian et al[239]	Melphalan (d)	35	17–19	18
	Melphalan, prednisone (i)	79	~65	24
Bergsagel et al[21]	Melphalan (d)	165	14	25
Bergsagel et al[189]	Melphalan, prednisone (i)	100	72	28
Costa et al[25]	Melphalan (d)	60	~25	26
	Melphalan, prednisone (d)	71	~48	35
	Melphalan, prednisone + testosterone (d)	58	~54	24
Hoogstraten et al[240]	Melphalan (d)	64	45	23
Hoogstraten et al[241]	Melphalan (i)	48	45	26
Korst et al[22]	Cyclophosphamide (d)	165	~48	24.5
McArthur et al[237]	Melphalan (d)	39	41	28
MRC 1st study[242]	Melphalan (d)	133	NR	18
	Cyclophosphamide (d)	141	NR	18
MRC 2nd study[243]	Melphalan, prednisone (d)	128	NR	20
	Cyclophosphamide (d)	124	NR	20
MRC 3rd study[244]	Melphalan (i)	179	NR	20
	Cyclophosphamide (i) (intravenous)	174	NR	26

* d, daily; i, intermittent; NR, not reported.
† Response rates shown with Myeloma Task Force Criteria or approximated from published data.

TABLE 56–10. Dosage Schedules for the M2, VMCP–VBAP, and ABCM Regimens

Drug Regimen	*Vincristine*	*Melphalan*	*Cyclophosphamide*	*BCNU*	*Doxorubicin*	*Prednisone*
M2 regimen[246]	0.03 mg/kg day 1	0.25 mg/kg days 1–7	10 mg/kg day 1	0.5 mg/kg day 1		1 mg/kg days 1–7
VMCP[190]	1.0 mg day 1	6 mg/m²/d days 1–4	125 mg/m²/d days 1–4			60 mg/m²/d days 1–4
VBAP[190]	1.0 mg day 1			30 mg/m² day 1	30 mg/m² day 1	
ABCM[248]		6 mg/m²/d days 1–4	100 mg/m²/d days 1–4	30 mg/m² day 1	30 mg/m² day 1	days 1–4

As currently used, the M2 protocol is usually repeated at 4- to 5-wk intervals. The VMCP–VBAP program repeats courses of chemotherapy in 21-day cycles using either a direct alternation of the two regimens or a syncopated alternation wherein VMCP is used for three cycles followed by VBAP for three cycles with similar therapeutic results by either of these schedules. Currently an every-3-week alternation is used. The MRC has used an almost identical schedule to VMCP–VBAP in their alternating program, except that vincristine and prednisone have been deleted. Alternations are also at 3-wk intervals in the MRC's ABCM program.

drug dosages that were essentially identical with that of SWOG, with the deletion of vincristine and prednisone (see Table 56–10).[248]

Slight changes in dosages of the M2 regimen have been used in various series.[206] With the M2 regimen, improved survival has been reported in a nonrandomized study, in which survival was calculated from the date of diagnosis rather than from the onset of therapy.[246] Subsequent randomized studies carried out by the Eastern Cooperative Group (ECOG) in the United States and by a multihospital group from Denmark compared the M2 regimen to melphalan and prednisone.[249,250] Both studies failed to show a survival advantage with the M2 regimen, although good-risk subsets in the ECOG study had improved survival.[249] An update on the ECOG study reported improved survival for stage III patients.[247]

Two successive studies carried out by SWOG compared the alternating combination regimens to a simpler regimen of MP or vincristine, cyclophosphamide, plus prednisone (VCP). In both studies (evaluated by different study coordinators), quite similar advantages in terms of improved response rate and improved median survival were observed with the alternating combination compared with the simpler regimen.[190,251] Results of the first of these studies were reanalyzed in 1985, again demonstrating a survival advantage of alternating combination chemotherapy over MP.[190,251] The second of SWOG's evaluations of alternating combinations demonstrated remarkably similar survival plots for the VMCP plus VBAP compared with the simpler VCP regimen. Analysis of pretreatment prognostic factors showed that the treatment groups were quite comparable. A significantly larger proportion of patients responded to the alternating combinations, suggesting that the additional responsive patients may have required combination therapy to reach remission status and could be anticipated to have had a poorer prognosis and below average remission duration. Analysis of the data on high-risk stage III patients in some studies supports this interpretation and is consistent with the overall remission duration in the VMCP-VBAP group being diluted with the addition of poor-risk patients "recruited into" the responsive category with the aggressive combinations who would not have achieved remission with the simple regimens.[246]

A similar interpretation may apply to studies from ECOG and the CALGB, who found improved response rates, survival time, or both in specific subsets of patients with multiagent combinations compared with the MP regimen.[249,252] In these two studies, overall survival for all patients was not improved, suggesting that the increased toxicity of the aggressive regimens may have a detrimental effect on survival of subsets of patients. The MRC study made a similar observation to that by SWOG. In the MRC study, 627 patients were randomized to receive almost identical schedules of the cytotoxic agents used in the SWOG VMCP-VBAP studies, except that vincristine and prednisone were omitted. The MRC study compared alternating MC and BA to M in a study begun in 1982 and closed in 1986. In the MRC's study, the survival advantage for the 314 patients receiving the alternating combinations was significantly superior (p=0.0003) to that obtained with M alone.[248] Curves for the MRC5 study are similar to the SWOG results despite the omission of vincristine and prednisone. The MRC's comparison of ABCM to M is significantly larger than the SWOG study or other studies comparing multiagent chemotherapy to M or MP.[248] A summary of results from these studies appear in Table 56–11.

Other multicenter randomized trials using VMCP-VBAP or variants of the M2 protocol (VBMCP) failed to show better results than simpler regimens (Table 56–12).[253] Comparison of the different trials is difficult because of different prognostic factors, differences in the treatments used, and differences in dose modifications and other factors. Several studies compared sequential administration of various alkylating agents with simultaneous combinations or MP (data not shown). These studies showed inferiority or no advantage for the sequential regimens.[188,252] Although there are discrepancies between multiagent and simpler regimens in various trails, none of these regimens are curative or control the disease for 4 years or longer. Therefore newer therapeutic approaches are needed.

Although INF-α is known to have some activity in mye-

TABLE 56–11. Results of Recent Alternating Combination Chemotherapy Regimens Used for Remission Induction in Multiple Myeloma in Multicenter Randomized Trials

*Investigations**	*Treatment*	*No. of Patients*	*% Responding† (mo)*	*Median Survival*
SWOG Alternating Combinations vs MP or VCP				
Study 7704[190,251]	VMCP + VBAP or VCAP	160	54	42
	MP	77	32	23
Study 7927[251]	VMCP + VBAP	93	54	48
	VCP	107	28	29
MRC Alternating Combination vs M				
Myelomatosis V[248]	ABCM	314	61	32
	M	316	59	24

* In these studies, patients had a statistically significant improvement in survival with alternating combination chemotherapy as compared with melphalan or MP therapy.
† Response criteria varied between SWOG and the MRC groups but were consistent within each group's trial.

loma patients in relapse, the recombinant forms of IFN-α have had only limited study in previously untreated patients.[219–222,259–261] In an initial report, 7 of 14 patients with previously untreated myeloma with stages I or II myeloma responded to treatment.[223] The response was associated with an increase in residual polyclonal immunoglobulins. However, two randomized trials comparing initial therapy with IFN-α to chemotherapy have shown IFN-α monotherapy to be less active than standard chemotherapy.[262,263] Recombinant IFN-α has also been integrated into combination chemotherapy with alkylating agent and prednisone combinations.[224] On the basis of the initial experience with this approach, the CALGB

TABLE 56–12. Results With Combination Chemotherapy Regimens Used for Remission Induction in Multiple Myeloma in Multicenter Randomized Trials That Failed to Show a Survival Advantage With Multiagent Chemotherapy Compared With Simple Alkylating Agent Regimens

Investigations	*Treatment*	*No. of Patients*	*% Response (mo)*	*Median Survival*
Argentine[255]	MeCCMVP	105	46	41
	MP	129	38	39
CALGB[254]	MCBP (I.V.)	156	56	29
	MCBPA (I.V.)	157	44	26
	MP (I.V.)	146	47	33
Canadian[189]	MCBP	116	47*	31
	MP	125	31*	28
Danish[250]	M2	31	45	21
	VMP	32	73	30
	MP	33	58	21
ECOG[256]	M2	134	74	~31
	MP	131	53	~30
Finnish[257]	MOCCA	64	75	41
	MP	66	54	45
Norwegian[258]	M2	33	74	33
	MP	34	67	33
SECSG[256]	BCP	186	49	36
	MP	187	52	36
Italian[253]	VMCP-VBAP	158	77	32
	MP	146	64	37

MeC, methyl-CCNU; B, BCNU; C, cyclophosphamide; V, vincristine; P, prednisone; A, doxorubicin (Adriamycin); MOCCA, melphalan, vincristine, CCNU, cyclophosphamide, doxorubicin.
* SWOG response criteria (all others reported by Myeloma Task Force Criteria).

initiated a randomized trial comparing the effectiveness of MP to MP plus recombinant IFN-α2.[261] There appears to be no advantage to using aggressive regimens in treatment of stage I patients. The major issue is whether any therapy should be employed until clear evidence of symptomatic disease progression occurs. Application of additional prognostic factors, such as the pretreatment β_2-microglobulin level or evaluation of the proliferative index of myeloma cells, may assist in better identifying the patient groups most likely to benefit from aggressive systemic therapy.

TUMOR CELL REDUCTION WITH INDUCTION CHEMOTHERAPY. The magnitude of tumor cell reduction with chemotherapy can be assessed using the quantitative methods to determine response in terms of the degree of cytoreduction achieved. For myeloma, this was first achieved using a computer-based method in which serial measurements of the amount of M-component produced per cell in vitro, intravascular mass of M-components, and catabolic rate were integrated.[2,170] For the current standard treatment programs and magnitude of cell death determined from M-component-derived measurements, the maximal degree of cytoreduction observed in patients treated with conventional chemotherapy rarely exceeds 90% to 99%. Despite continued treatment, the tumor burden appears to plateau in most cases.[170] Kinetic analysis of the plateau-phase population suggests that the residual tumor cells behave differently from those present before treatment, and they are comparatively hypoproliferative and perhaps less responsive to cytotoxic chemotherapy.[209]

With a total tumor burden in most patients in the range of 10^{12} myeloma cells or more, it is not surprising that there is not a strong correlation between the exact magnitude of cytoreduction (*e.g.*, 75%, 90%, 99%) and overall survival. However, remission durations after induction chemotherapy can vary substantially in comparably staged patients with similar degrees of apparent cytoreduction and the presence of a clearly measurable residual M-component peak in the serum. Although the median duration of unmaintained remission is 11 months, unmaintained remissions after induction chemotherapy in some patients with stage III myeloma may last for 5 years or longer.[264,265] This suggests that there is an alteration in the residual myeloma cell population or in the tumor-host relation. Such observations provide the basis for seriously questioning whether the residual cell mass determined from M-component levels in remission reflects the initial population of malignant plasma cells or a less malignant population more akin to that in patients with MGUS. However, patients regularly relapse with overt myeloma from unmaintained remissions, indicating that an underlying highly malignant monoclone persists but may be submerged under a population of less highly proliferative M-component-secreting cells.

Analysis of the myeloma regrowth rate based on M-component doubling times has been carried out for patients studied sequentially after a series of unmaintained remissions.[169] Even in the presence of continued chemosensitivity (as reflected by cytoreduction after reinstitution of chemotherapy), some patients studied developed a progressive shortening of the M-component doubling time during subsequent unmaintained remissions. Such observations suggest progressive loss of growth control with the emergence of a kinetically more aggressive tumor cell population.

Remission Maintenance Versus Unmaintained Remission

Therapeutic approaches in myeloma have usually been developed in an analogous fashion to those for other advanced neoplasms and have included remission-induction phase and remission-maintenance phase treatments. Myeloma patients who exhibit drug sensitivity and achieve remission usually have been maintained on a similar form of chemotherapy until the time of relapse.

The usefulness of maintenance therapy with cytotoxic drugs has been examined in several studies with similar results.[264,266–268] Patients achieving remission with chemotherapy were randomized to maintenance chemotherapy with MP or to no maintenance therapy. Patients randomized to no maintenance received alkylating agent chemotherapy again at the earliest evidence of relapse as manifested by a rise in M-component levels or recurrent symptoms and signs of active myeloma. There was no overall survival advantage for patients receiving maintenance chemotherapy. Continuation of conventional alkylating agent therapy for patients achieving remission appears to offer no obvious advantage over unmaintained remission, as long as patients are followed closely and have treatment reinstituted when there is laboratory or clinical evidence of reactivation of myeloma. In general, patients followed in unmaintained remission should be followed monthly, with regular monitoring of serum and urine M-components to detect the first signs of relapse. Patients presenting initially with stage III myeloma with heavy Bence Jones proteinuria or amyloidosis must be followed closely, because fulminant relapse from unmaintained remission can lead to irreversible complications unless treatment is reinstituted promptly at the first sign of disease reactivation.

An approach to remission maintenance that used recombinant IFN-α was reported by the Italian Multiple Myeloma Study Group.[269,270] In this study, 70 patients with remissions induced with MP or VMCP-VBAP (on a randomized induction) were re-randomized to maintenance therapy with recombinant IFN-α2 or to no treatment. The IFN-α2 was administered at a dosage of 3×10^6 IU/m^2 subcutaneously three times weekly. After 27 months of follow-up, 8 (24%) of 33 of evaluable patients receiving IFN-α2 and 22 (59%) of 37 patients with no maintenance had relapsed, with a significant difference ($p<0.01$) in the actuarial curves of remission duration in the two groups.[270] A larger study of IFN maintenance conducted by the SWOG with over 200 patients randomized to interferon maintenance or observation using 3×10^6 of IFNα2 given intravenously with the same schedule showed no advantage of IFNα2 over unmaintained remission for remission duration or survival.[271] Further follow-up of these two studies and several other interferon maintenance studies are required before the role for IFN maintenance can be established.

SOLITARY PLASMACYTOMA OF BONE AND EXTRAMEDULLARY PLASMACYTOMA

About 7% of all patients with plasma cell malignancies present with solitary lesions in bone or soft tissues, with bone marrow

examinations demonstrating fewer than 5% plasmacytes. Several factors differentiate patients with solitary lesions from those with multiple myeloma. Age at presentation tends to be younger, and a higher percentage are male (70% versus 55%). A smaller fraction (30% versus 97%) present with serum or urinary M-components.

The demonstration that an elevation in M-component may persist after high-dose local irradiation, but may return to normal with subsequent long-term disease-free survival after nonradical surgical excision of Waldeyer's ring material, suggests two alternative possibilities for the response of certain malignant plasma cells to irradiation. One alternative is that a substantial population of cells in certain patients is highly resistant to irradiation. However, several factors mitigate against this explanation, especially the long disease-free survival after a nonradical surgical approach. Because of the monoclonal nature of the disease in these patients and their generally excellent response to irradiation, it seems more likely that these persistent cells represent clonogenically nonviable foci that fail to manifest radiation damage because they divide slowly or not at all. Such behavior is somewhat analogous to functioning pituitary adenomas in which elevated hormone levels may be observed for months or years after radiation therapy without evidence of ultimate progression.

Several studies have shown a relatively favorable course for both these groups of patients, but many long-term studies have demonstrated the distinct difference in ultimate prognosis between patients with solitary lesions in bone and those with extramedullary lesions.[272-275,277] Although they experience significantly longer survivals than patients with classic multiple myeloma, virtually all patients with solitary bone lesions develop systemic disease if followed for sufficient periods.[272-275] In one study, although almost 35% of patients were progression-free at 10 years, by 13 years, more than 90% of patients experienced widespread evidence of disease.[274] The report by Chak and coworkers is slightly more optimistic.[276] More than 80% of patients treated for extramedullary lesions are progression free at periods exceeding 10 years after treatment.[272-274,277]

Despite this difference in ultimate prognosis, long-term survival is observed in substantial numbers in both groups and suggests the desirability for long-term local control. Radiation doses of 3500 to 5000 cGy have been proposed, with doses at the lower end of this spectrum usually applied with shortened treatment times and increased daily radiation fractions. We favor a total dose of 4500 to 5000 cGy in 4.5 to 5 weeks, using megavoltage fields that adequately encompass necessary soft tissue and bony structures. In primary bony lesions, the entire medullary cavity of the bone must be encompassed, as in patients with Ewing's tumor because of the possibility of medullary cavity spread.

Few data are available on the probability of regional lymph node spread, and treatment of nodal sites, in addition to adequately encompassing of the primary lesion, usually is not recommended. The report of Knowling and associates suggests that treatment may be of value in selected patients.[273] Typical survival curves after radiation treatment for these two groups of patients appear in Figure 56–9.[272-274,276,277]

IN VITRO TESTING OF CLONOGENIC MYELOMA CELLS

In vitro methods have been developed to support the growth of colony-forming neoplastic plasma cells from the bone marrows of some patients with multiple myeloma and to assess the response of the clonogenic myeloma cells to a variety of anticancer drugs.[59,278-281] Clonogenic growth of myeloma cells has been applied to in vitro drug testing by several laboratories.[278,279,281,282] At the Arizona Cancer Center, true-positive correlations between in vitro sensitivity and clinical response were obtained in 22 (79%) of 28 instances in which in vitro sensitivity was observed, and true-negative correlations with in vitro drug resistance were observed in 35 (99%) of 37 instances.[281] Although such findings suggest that this assay may have potentially broad application, it is still applicable to only a few of the patients tested, because of inadequate colony growth in many instances. Due to technical limitations, it is currently impractical to routinely test patients' myeloma cells for drug sensitivity. However, in the research setting, we continue to find this approach an aid in the discovery of new drugs with activity against myeloma cells and in identifying potentially active drugs for a selected subset of patients whose cells can be cultivated in vitro. New information on cytokines that support the growth of plasmacytoma cells and the use of more sensitive assays may increase the applicability of this approach to myeloma in the future.[61,63,283-285]

TREATMENT OF REFRACTORY MYELOMA

Patients who relapse after unmaintained remission can often be reinduced into remission with a regimen similar to that used initially and are not considered to be refractory to therapy

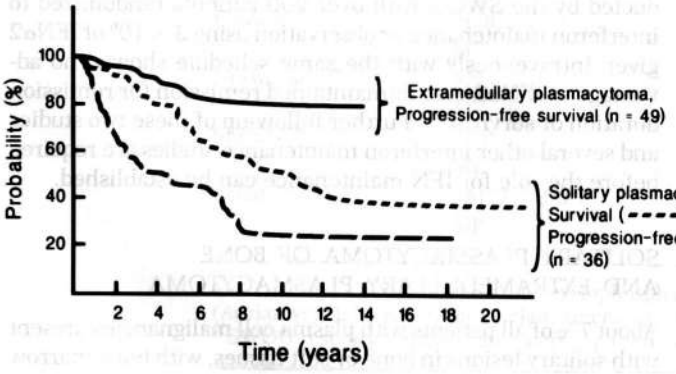

FIGURE 56–9. Survival and disease-free survival for patients with solitary plasmacytoma of bone and disease-free survival of those with solitary soft-tissue disease. Notice the significant advantage for those with soft tissue disease and low disease-free survival (in time) for those with bone disease.

unless they fail to achieve remission on reinduction.[264,286] However, at least one third of patients with multiple myeloma fail to respond to induction chemotherapy, and those who initially achieve remission eventually relapse and require additional treatment. Standard and new agents and approaches have been evaluated in refractory patients.[287,288] Therapeutic agents used for treatment of refractory patients usually include the same drugs used in initial remission-induction therapy (*e.g.*, anthracyclines, glucocorticoids, vinca alkaloids, alkylating agents, nitrosoureas), often given in alternative dosages, schedules, and combinations to those used initially. INF-α has activity as a phase II agent, but remissions are usually short, and IFN-α has yet to be integrated effectively into combination therapy for second-line therapy.[221,222,289–291]

It is important to differentiate between the two subsets of patients who are usually classified as refractory, because their prognoses differ substantially. For simplicity, refractory myeloma patients are usually divided into drug-resistant and relapsing groups. Patients who fail to respond to induction chemotherapy and are drug-resistant have the poorest overall prognosis, and only a few respond to alternate treatments. The second major category comprises relapsing patients who respond to induction chemotherapy but then relapse while still receiving chemotherapy or within a few months thereafter. They have a higher probability of responding to second-line therapy than do the drug-resistant patients.

High-Dose Glucocorticoids

The antitumor activity of single-agent prednisone for a high-dose, alternate-day schedule for resistant and relapsing patients was first reported over 20 years ago.[23] This single-agent activity of high doses of glucocorticoids has been confirmed and extended using prednisone and dexamethasone in alternate-day or pulse schedules.[214,287,292,293] High-dose dexamethasone recently has been studied in previously untreated patients with myeloma and has been found to be active when used as monotherapy.[293a] A P-glycoprotein-expressing multidrug-resistant myeloma cell line was reported to develop collateral sensitivity to glucocorticoids, suggesting that there may be some specificity of steroids for drug-resistant cells.[294] Overall, approximately 40% of resistant and relapsing myeloma patients achieve second remissions with glucocorticoids. Because glucocorticoids are nonmyelosuppressive, they are particularly useful in refractory patients with poor bone marrow reserves. In our experience, some pancytopenic patients have remissions of myeloma for several years with alternate-day prednisone alone. Efforts have been made to quantitate glucocorticoid receptors in myeloma, and these measurements may aid in identifying patients potentially sensitive to glucocorticoids.[295]

Combination Chemotherapy Regimens

Although there were a few initial favorable reports on combination regimens that included primarily alkylating agents, most reports have been less promising, with response rates in the range of 8% for resistant and 22% for refractory patients.[246,297–302] These regimens are far more active for reinducing remissions in patients who have disease reactivation from unmaintained remission.[264,286,303–305]

More favorable results have been obtained with doxorubicin-based combinations. Although doxorubicin alone exhibits activity in only 10% of patients, when combined with BCNU or with BCNU, vincristine, and prednisone (VBAP) or cyclophosphamide instead of vincristine, somewhat better results are obtained.[27,306–310] Approximately 30% of relapsing patients respond to these regimens, but only 10% of resistant patients respond. Although not all studies report the remission durations of responders or overall survival, the remission duration is usually less than 1 year. Significantly better results have been obtained by using the vincristine, doxorubicin, and dexamethasone (VAD) regimen developed at the M.D. Anderson Cancer Center.[311] Vincristine and doxorubicin are administered by continuous infusion over 4 days through an indwelling venous catheter, and dexamethasone is given orally (Table 56–13).

In an initial report, 14 (70%) of 20 patients with refractory myeloma responded to VAD, with a projected survival in excess of 1 year for responders.[311] Although granulocytopenia was only moderate, infection represented the most frequent complication, perhaps because of the large doses of dexamethasone used. In a follow-up report, VAD or dexamethasone were administered on a nonrandom basis to 85 refractory patients.[214] Among relapsing patients, 65% responded to VAD, but only 21% responded to dexamethasone alone. Among resistant patients, only 32% responded to VAD, a result quite similar to the 27% response rate observed with dexamethasone alone. This suggests that response to the VAD regimen in initially unresponsive patients is primarily due to the glucocorticoid in the regimen.[214] Similar therapeutic results have been confirmed with the VAD regimen by other investigators.[312–314] Toxicity has been the major limitation of the VAD regimen, with serious infection attributed primarily to the steroid program. Serious gastrointestinal toxicity, including gastric perforations, and steroid psychoses have been observed. Overall, approximately one third of patients receiving VAD develop moderate to severe toxic effects. Nonetheless, it appears to be the most effective treatment for myeloma relapses.

For patients with primary drug resistance, steroid alone is preferable to VAD. The multidrug resistance mechanism associated with P-glycoprotein expression appears to be frequently expressed by myeloma cells from patients with drug-resistant disease.[329–331] A novel means for reversing resistance to VAD has been reported for relapsing patients who previously

TABLE 56–13. Dosage Schedule for VAD Regimen

Vincristine	0.4 mg/d I.V. for 4 d
Doxorubicin	9 mg/m^2/d I.V. for 4 d
Dexamethasone	40 mg/d orally for 4 d beginning on days 1, 9, and 17 of the first 28-d cycle and on alternate cycles thereafter. On the other cycles dexamethasone is given only on days 1–4.

All patients also received cimetidine for antacid prophylaxis and trimethoprim—sulfamethoxazole as antiinfective prophylaxis.

(Barlogie B, Smith L, Alexanian R. Effective treatment of advanced multiple myeloma refractory to alkylating agents. N Engl J Med 1984;310:1353–1356)

responded to the VAD regimen and subsequently developed multidrug resistance associated with expression of the P-glycoprotein.[315] The P-glycoprotein was detected using a murine monoclonal antibody and by mRNA dot blot analysis. Five refractory myeloma patients were first treated with the VAD regimen, and at the time of relapse or failure to respond to VAD, the calcium channel blocker verapamil was administered at high dosage by continuous infusion along with VAD. Resistance was at least partially reversed in 2 patients, with improvement in M-component and hematologic values. In one patient whose myeloma cells were tested in vitro, verapamil exposure significantly increased intracellular accumulation of doxorubicin, suggesting a possible mechanism by which the verapamil effect was mediated. In a subsequent expansion of this trial, 5 (23%) of 22 VAD-refractory patients achieved remission again after high-dose intravenous verapamil was added to the VAD regimen.[316] However, verapamil is not a good agent to use as a chemosensitizer in myeloma patients, because it induces hypotension that can further compromise renal function in patients with Bence Jones proteinuria and impaired renal function. These studies provide proof that multidrug resistance can be circumvented, but better chemosensitizers are needed. Recently, cyclosporin also has been reported to reverse multidrug resistance when combined with the VAD regimen for use in VAD-resistant myeloma patients.[331a]

SYSTEMIC RADIATION THERAPY

Rider, Bergsagel, and colleagues were instrumental in pioneering wide-field or hemibody irradiation for systemic illness.[317,318] A variety of treatment schemes have been used, but in most, a radiation dose of 750 to 850 cGy in 150-cGy fractions (dose rate of ≥50 cGy/minute) is given to the hemibody (umbilicus used as midpoint) after pretreatment preparation with corticosteroids and antiemetics. Total-body approaches have also been used.[233] Patients have usually been a a poor-prognosis group with stage III disease, who have usually relapsed after first-line chemotherapy.[206] In most patients, the lower hemibody was treated initially. Approximately 50% to 75% of patients complete treatment to hemibody segments in most series.[317,318,320–325]

Because of the incidence of radiation pneumonitis in patients treated initially, cumulative lung doses have been reduced to 600 to 650 cGy (usually not corrected for air transmission) in more recently treated patients.[326] Although laboratory evidence of hematologic toxicity exists for most patients who have received treatment to the whole body, with some patients requiring platelet or erythrocyte transfusions, major clinical morbidity from hematologic toxicity has been moderate. In some instances, it can be prolonged. By using this irradiation approach, approximately half of all treated patients have experienced significant subjective relief.

Median survivals in irradiated patients have averaged 6 months, with mean survival times averaging 12 months. Some patients from this group have survived more than 18 months, and two reports documented more than 24 months of survival in several patients.[327,328]

In an attempt to use this treatment modality for better-prognosis patients, the SWOG carried out a phase III prospectively randomized trial (SWOG 8229/8230) in which previously untreated patients who achieved remission (≥75% tumor mass regression) randomized to maintenance chemotherapy or to sequential hemibody irradiation (750 cGy per five fields for 1 week) with 4 to 6 weeks or more elapsing between the two irradiation courses, depending on the severity and duration of hematologic toxicity.[206]

In the SWOG study, the survival outcome for patients receiving hemibody irradiation was significantly inferior to that of patients receiving maintenance chemotherapy. The difference in survival could be attributed to a shorter relapse-free survival with irradiation. Survival time from relapse to death was identical in both groups.[206,319] Myelosuppression was significantly more severe in patients receiving hemibody radiation therapy than those receiving maintenance chemotherapy. The primary toxicity was prolonged thrombocytopenia. These findings indicate that chemotherapy maintenance is more effective than hemibody irradiation for remission consolidation in myeloma patients who respond to induction chemotherapy.

HIGH-DOSE THERAPY ALONE OR WITH BONE MARROW TRANSPLANTATION

More aggressive approaches to the therapy of multiple myeloma use high-dose chemotherapy alone or high-dose chemotherapy with total-body irradiation and autologous or allogeneic bone marrow transplantation to overcome drug resistance to conventional-dose therapy.[332–346] The drug most commonly used in high doses has been melphalan, administered intravenously in doses ranging from 80 to 140 mg/m^2, without or with bone marrow or peripheral blood stem cell support. With high-dose melphalan alone, a high response rate is observed, including complete remissions associated with complete disappearance of the M-component and normalization of the bone marrow.[338] Unfortunately, the responses to high-dose melphalan alone among relapse patients have usually lasted only 3 months to 1 year. Toxicity has included profound myelosuppression, mucositis, diarrhea, nausea, and vomiting. Treatment-related deaths are not uncommon and are associated with host failure and severe hematologic toxicity. However, because the use of high-dose melphalan is still relatively new, further experience may provide a means to enhance efficacy and reduce toxicity (*e.g.*, with the use of myeloid colony-stimulating factors or by limitation of high-dose melphalan administration to patients with good performance status).

Prognostic factors associated with better outcome with autologous bone marrow transplantation in myeloma include the presence of drug-sensitive disease.[347] The addition of autologous bone marrow transplantation with or without purging has reduced the severity of myelosuppression. When total-body irradiation (usually 200 cGy twice daily for 3 days; total dose, 1200 cGy) delivered at a reduced dose rate (5–50 cGy/minute)) was combined with high-dose melphalan and autologous bone marrow transplantation, significantly longer remissions were observed.[339] In many instances, evidence of a residual M-component was still detected with immunofixation. Efforts to develop purging techniques to remove residual myeloma from the marrow are being attempted to enhance the potential of autologous transplantation. As an alternative to purging, autologous blood stem cells have been used for hematopoietic reconstitution.[348–353] The main limitation appears

to be the difficulty of eradicating myeloma with the available preparative regimens for transplantation.

A promising study of 90 patients was published by the European Cooperative Group for Bone Marrow Transplantation.[354] This study showed good outcome for a significant fraction of patients receiving HLA-matched sibling donor marrow. The complete remission rate after marrow transplantation was 43% for all patients and 58% for patients with engraftment. The actuarial survival rate at 76 months was 76% (Fig. 56–10). Of 90 patients undergoing allogeneic bone marrow transplantation, 43% of all patients and 58% of patients who engrafted achieved complete remission. The median duration of relapse-free survival for complete remission patients was 48 months, and overall survival at 76 months was 40% (see Fig. 56–10). Allogeneic transplantation should be considered for selected patients younger than 55 who have an HLA-matched sibling donor.

ACTIVITY OF AGENTS IN PHASE II TRIALS

A few other antitumor agents have induced remissions in 10% or more of myeloma patients in relapse in phase II trials. These include pentostatin,[356] epirubicin, poly (I,C)-LC (an interferon inducer), peptichemio, and teniposide.[355,357–360] Except for the interferon inducer, these agents warrant additional investigation in refractory cases to better define their activity.

Other chemotherapeutic agents that have been subjected to phase II clinical trials in myeloma and found to have minimal activity (with less than a 10% response rate in refractory patients) include aclarubicin, acronine, amsacrine, bleomycin, cisplatin, chlorozotocin, cytarabine, diaziquone, etoposide, hexamethylmelamine, mitoxantrone, prednimustine, procarbazine, pyrazofurin, urethane, vindesine, fludarabine, or amonafide.[19,361–380] Although hexamethylmelamine appeared to exhibit greater than 10% activity, this was probably attributable to the concomitant use of glucocorticoids in the protocol.[381]

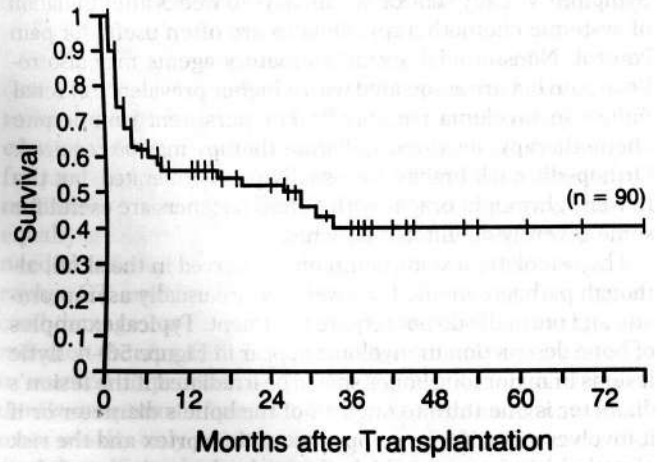

FIGURE 56–10. Actuarial survival after bone marrow transplantation for all 90 patients reported from the European Group for Bone Marrow Transplantation Registry as having allogeneic transplants performed for multiple myeloma. The actuarial survival at 76 months was 40%. The median duration of relapse-free survival among patients who were in complete remission after their transplants was 48 months. (Gahrton G, Sante T, Per L, et al. Allogeneic bone marrow transplantation in multiple myeloma. N Engl J Med 1992;325:1267–1273)

COMPLICATIONS AND SPECIAL PROBLEMS

RENAL FAILURE

In most studies, approximately 20% of patients with multiple myeloma present with renal failure, which adversely affects survival.[382] In one report, patients with stage IIIB myeloma had a median survival of only 4 months.[383] For patients who have normal or minimally impaired renal function, it is important to take actions that minimize the likelihood of subsequent development of renal failure. Myeloma patients should have a high fluid intake (*e.g.*, at least 2 L/day) to facilitate the excretion of calcium, Bence Jones proteins, uric acid, and other nephrotoxic excretory products. Patients with Bence Jones proteinuria and evidence of advanced or progressive myeloma should promptly be started on a chemotherapy regimen.

Adequate chemotherapy and hydration are important in managing myeloma patients with renal failure.[382] Administration of allopurinol with chemotherapy is a worthwhile precaution in stage III patients, at least for the first few courses of therapy. Patients with known myeloma should not be dehydrated for intravenous pyelography, and hypercalcemia and urinary tract infections should be treated promptly. The use of antibiotics with known nephrotoxicity (*e.g.*, the aminoglycosides) should be avoided if possible. Agents causing sustained hypotension and reduced renal blood flow should also be avoided. When melphalan is administered intravenously to patients in renal failure, increased myelosuppression has been observed.[384] Pharmacokinetic studies of intravenous melphalan in dogs and of oral administration in myeloma patients established that melphalan elimination is reduced by renal insufficiency.[385,386] Dose reductions are often needed for melphalan when it is administered intravenously, but because of the varying bioavailability of oral melphalan, dose reductions for renal failure may further compromise its therapeutic activity.

In the fourth MRC myeloma chemotherapy trial, management of renal failure was studied prospectively.[387] Of the 522 patients admitted to the trial, 80 had evidence of renal failure that persisted after an initial 24-hours of rehydration. Seventy-three of the 80 patients who had renal failure were maintained with a fluid intake of at least 3 L/day in addition to receiving chemotherapy. These patients were randomized to receive sodium bicarbonate or no supplement to render the urine pH neutral. The remaining 7 patients had congestive heart failure or required continued dialysis for oliguric renal failure and were not eligible for evaluation of oral fluid supplementation. Of 49 patients who survived more than 100 days, 39 achieved reversal of renal failure (18 complete, 21 partial). Death of 14 of the patients was directly attributable to renal failure rather than other complications or manifestations of myeloma. Patients who received bicarbonate did marginally better than those who did not. The survival outcome of patients with renal failure in the MRC's third myeloma trial appeared to be inferior to that obtained in the fourth trial, in which high fluid