Pharmacologic Principles of CANCER TREATMENT

Bruce Chabner, M.D.

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重庆医科大学附属第一医院图书馆藏专用章

1982

W. B. Saunders Company

Philadelphia London Toronto Mexico City Rio de Janeiro Sydney Tokyo

W. B. Saunders Company: West Washington Square
Philadelphia, PA 19105

1 St. Anne's Road
Eastbourne, East Sussex BN21 3UN, England

1 Goldthorne Avenue
Toronto, Ontario M8Z 5T9, Canada

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Artarmon, N.S.W. 2064, Australia

Ichibancho, Central Bldg., 22-1 Ichibancho
Chiyoda-Ku, Tokyo 102, Japan

Library of Congress Cataloging in Publication Data

Main entry under title:

Pharmacologic principles of cancer treatment.

1. Cancer—Chemotherapy. 2. Antineoplastic agents.
I. Chabner, Bruce. [DNLM: 1. Neoplasms—Drug therapy.
AZ 267 C427p]

RC271.C5P48 616.99'4061 81-40737

ISBN 0-7216-2477-4 AACR2

Pharmacologic Principles of Cancer Treatment ISBN 0-7216-2477-4

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Last digit is the print number: 9 8 7 6 5 4 3 2 1

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PREFACE

The development and successful use of drugs for treating cancer in the past three decades have provided the basis for a new subspecialty in internal medicine—medical oncology. No other field of medicine is more closely tied to a laboratory discipline than this. The interdependence between medical oncology and antineoplastic pharmacology is evident in every phase of cancer treatment from protocol planning to dose modification, drug level monitoring, and new drug evaluation.

This new book was undertaken in recognition of the importance of antineoplastic pharmacology in cancer treatment. It attempts to provide a comprehensive and detailed examination of the preclinical and clinical pharmacology of antineoplastic drugs. Given the rapid growth of knowledge in this field, this objective is beyond the capabilities of any one author. For this reason I sought the help of a number of knowledgeable contributors, chosen for their grasp of both the laboratory and the clinical aspects of these drugs. These co-authors deserve my most sincere appreciation for their patience during the tedious process of revising, editing, and proofreading their manuscripts. Equally deserving of my thanks are Mary Cowell and her staff at W. B. Saunders, and my editorial assistant Kathleen Moore.

We all hope that the final product will serve to enlighten, inspire, and encourage those committed to the belief that cancer will ultimately yield to drug therapy.

BRUCE A. CHABNER, M.D.

ACKNOWLEDGMENTS

This book has come into being through the efforts of a number of key individuals who are not recognized elsewhere in the text but deserve equal credit for the final product. Foremost has been Kathleen Moore, my able secretary and editorial assistant, whose tireless efforts to produce perfect copy made the job of writing and editing easier for all of us. My editor at Saunders, Mary Cowell, and my copy editor, David Harvey, ably molded the diverse individual contributions into a coherent whole. To my clinical colleagues at the National Cancer Institute, to my dedicated co-workers in the laboratory, and especially to my fellow pharmacologists Drs. Charles Myers, David Johns, and Joseph Bertino I owe particular gratitude for stimulating my personal interest in this field and suggesting the seemingly limitless applications of pharmacology to the problem of cancer treatment. And finally I want to thank my family for their patience and understanding during my years of occupation, and preoccupation, with this work; their indulgence of my interest in cancer pharmacology gave me the time and encouragement to finish this book.

CONTENTS

INTRODUCTION

In the past 30 years, since the discovery of antifolates and their introduction as effective antileukemic agents, drug therapy has truly revolutionized the treatment of malignant disease. Curative treatments have been discovered for many of the cancers that afflict children and young adults, including acute lymphocytic leukemia, Hodgkin's disease, testicular carcinoma, and others. These advances have generated great interest in every phase of drug research, leading to the development of a body of knowledge known formally as antineoplastic pharmacology. This field of research deals with the isolation, chemical and biochemical characterization, and experimental and clinical use of drugs for treatment of cancer.

Additional research efforts have been directed toward identifying new classes of active agents, chemically modifying known active drugs for the purpose of eliminating unwanted side effects, and determining the biochemical basis for selectivity of drug action against malignant cells. The resulting body of knowledge not only is useful to the experimental pharmacologist, but has a direct bearing on the design of clinical regimens and the understanding of drug effects, both toxic and therapeutic, in man. It is our purpose in this book to present a comprehensive examination of the experimental and clinical properties of antineoplastic agents in a form understandable to both experimentalists and clinicians.

The introductory chapters provide a background of general principles of drug action and usage. Thus, topics such as drug transport, cellular pharmacology, cell kinetics, pharmacokinetics, and principles of drug level monitoring are considered in detail. These topics are essential to the understanding of subsequent chapters, which deal with specific classes of clinically effective antineoplastic agents. Compounds of unproved value and those that have failed to show activity in clinical trial receive attention only to the extent that their experience has relevance to the use of active agents. The scope of this work does not include immunotherapeutic compounds. The level of presentation for each of these subjects is rigorous, but the text is intended for both a laboratory and a clinical audience.

It is with some hesitation that I and my co-authors have undertaken this project in view of the explosive pace of research in the cancer drug field. Nevertheless, we feel that a synthesis of both principles and facts, as found in this text, can serve as an important landmark in the cancer research effort in much the same way that a conference serves as both an ingathering and a point of departure. Thus, we hope that this book will stand as a measure of dramatic recent progress in our young field as well as a signpost to indicate the direction of future research.

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Section I

1 THE ROLE OF DRUGS IN CANCER TREATMENT

Bruce A. Chabner

The treatment of cancer, more than that of any other disease, requires the cooperative efforts of widely divergent medical specialties. Although cancer has been for centuries the concern of the surgeon, new treatment approaches have created important roles for the radiotherapist and internist in the management of cancer patients, and have placed the decision-making process in the hands of these new specialists. Steps in the treatment decision-making process are discussed in this chapter in order to provide the reader with an understanding of the overall role of drugs in cancer therapy.

DETERMINANTS OF TREATMENT PLANNING

The primary determinant of treatment is the histologic diagnosis. Malignant neoplasms occur in over 100 different pathologic forms, each with a characteristic natural history, pattern of progression, and responsiveness to treatment. Thus, the *histologic diagnosis,* usually made by surgical excision of a primary tumor or metastasis, is of critical importance as a first step in treatment planning. The clinical oncologist must be alert to the possibility of atypical presentation of treatable and even curable tumors, such as germ cell tumors of the testis. For example, germ cell tumors on occasion may arise in the thoracic or abdominal cavity in the absence of a primary testicular tumor, but these unusual presentations retain the same excellent response to appropriate chemotherapy.[1] In certain cases — as, for example, bronchogenic carcinoma or the non-Hodgkin's lymphomas — accurate histologic *subtyping* of tumors is important, since the subtypes of these diseases have different patterns of clinical response to treatment. Subtyping may require the characterization of cell surface immunologic markers, for example, to distinguish T- and B-cell lymphomas, or the identification of specific intracellular secretory granules or enzymatic markers such as dopa decarboxylase in small cell carcinoma of the lung. The essential point is that the precise histologic identity of a tumor is the single most important determinant of treatment choice and patient management. Blind treatment, in cases lacking a histologic diagnosis, is rarely successful.[2]

The next step in treatment planning is to determine the extent of disease, and specifically to determine whether the tumor is curable by local treatment measures such as surgery or radiation therapy. The process of determining the extent of disease is termed *staging,* and plays an important role in making therapeutic choices for diseases that are responsive to multiple types of treatment. For example, malignant lymphomas are curable with radiotherapy in most cases if the tumor is confined to one lymph node region (Stage I). More extensive lymph node involvement or dissemination to extranodal sites necessitates treatment with more intensive and broadly applied therapies, usually chemotherapy. The specific combination of

therapies used depends on a number of factors, including the susceptibility of the particular type of neoplasm to drug or radiation therapy, and the patient's probable tolerance of the side effects and complications of the various possible treatments. Thus, while curative chemotherapy regimens exist for a substantial fraction of patients with diffuse histiocytic lymphoma, not all patients with this diagnosis are suitable candidates for intensive treatment. Those with underlying medical problems — e.g., heart disease, diabetes, or chronic pulmonary disease — might well suffer severely disabling or fatal complications from potentially curative regimens, as indicated in Table 1–1. In such cases the physician must weigh the chances of successful treatment against the probability of serious side effects from each of the therapeutic alternatives. The ultimate decision must be based on a thorough understanding of the *basic* and *clinical* pharmacology of the drugs in question, as well as an appreciation of the potential benefits and risks of alternative forms of treatment, such as radiotherapy and surgery.

DRUGS IN CANCER TREATMENT

Although drugs represent a relatively recent addition to the complement of weapons available for treating cancer, they are now employed at some time during the course of the illness of most cancer patients. Patients who have metastatic disease at the time of diagnosis usually undergo a surgical biopsy to establish the diagnosis. They may also undergo resection or irradiation of the primary tumor if the mass is producing incapacitating or potentially lethal local complications, such as obstruction of the bile duct, gastrointestinal tract, or respiratory tract. At this point, if malignant disease remains, drug treatment becomes the primary mode of treatment, offering either palliation, as in the case of most adenocarcinomas, or possible cure for lymphomas, testicular cancer, and other neoplasms (see Table 1–2).

Drug treatment regimens are based on a number of considerations. These include cell kinetic, pharmacokinetic, and biochemical-pharmacologic considerations; predictive *in vitro* tests; and, most important, prior empirical knowledge of the responsiveness of the pathologic category of tumor to specific drugs. These topics are considered in detail in succeeding chapters, but are reviewed briefly at this juncture in order to illustrate the broad range of factors that influence the planning of drug treatment regimens.

The Kinetic Basis of Drug Therapy

The objective of cancer treatment is to reduce the tumor cell population to zero cells. Chemotherapy experiments employing rapidly growing transplanted tumors in mice have established the validity of the *fractional cell kill hypothesis*. This states that a given drug concentration applied for a defined time interval will kill a constant fraction of the cell population, independent of the absolute number of cells. Thus, each treatment cycle kills a specific fraction of the remaining cells. The results of treatment are a direct function of (1) the dose of drug administered and (2) the frequency of repetition of treatment.

Most current chemotherapy regimens are

TABLE 1–1. Toxicity of BACOP Regimen for Treating Diffuse Histiocytic Lymphoma[33]*

Drugs	*Toxicity*	*Patients at Increased Risk*
Bleomycin	Pulmonary fibrosis	Chronic pulmonary disease; elderly
Doxorubicin (Adriamycin)	Cardiomyopathy; myelosuppression	History of heart disease; elderly
Cyclophosphamide	Hair loss; cystitis; myelosuppression	None
Vincristine (Oncovin)	Motor-sensory neuropathy	Elderly
Prednisone	Decreased glucose tolerance	Diabetic

*Risk of drug toxicity will also be increased in patients with compromised ability to eliminate a drug owing to renal (bleomycin) or hepatic (doxorubicin, vincristine) dysfunction. In general, elderly patients are at increased risk of toxicity because of underlying medical problems and possibly lower rates of drug elimination.

TABLE 1–2. Curability of Cancer with Drugs

Disease	*Therapy*	*Probable Cure Rate*
ADULTS		
Diffuse histiocytic lymphoma (stages III and IV)	Combination chemotherapy	40% or greater
Hodgkin's disease (Stage III or IV)	Combination chemotherapy	50% or greater
Testicular carcinoma (Stage III)	Combination chemotherapy ± surgery	50% or greater
Gestational choriocarcinoma	Methotrexate ± actinomycin D	90%
Ovarian carcinoma	Alkylating agents or combination chemotherapy	10%
Acute myelocytic leukemia	Combination chemotherapy	10%
CHILDREN		
Acute lymphocytic leukemia	Combination chemotherapy and cranial irradiation	50% or greater
Burkitt's lymphoma	Cyclophosphamide or combination chemotherapy	50% or greater
Wilms' tumor	Surgery, chemotherapy, and irradiation	50% or greater

based on these considerations and employ cycles of intensive therapy repeated as frequently as allowed by the tolerance of dose-limiting tissues such as bone marrow or gastrointestinal tract. The object of these cycles is to reduce the absolute number of remaining tumor cells to zero (or less than one) through the multiplicative effect of successive fractional cell kills [$(10^{11}$ cells) $\times$ $0.01 \times 0.01 \times 0.01. \ldots$]. In treating the large and kinetically heterogeneous tumors found in man, the fractional cell kill hypothesis probably does not apply as well as in the animal tumor models. Most clinical neoplasms are recognized at a stage of decelerating growth that is due to poor vascularity, competition for nutrients, and other unidentified factors. These tumors contain a high fraction of slowly dividing or nondividing cells (termed G_0 cells). Since many antineoplastic agents are most effective against rapidly dividing cells, the initial kinetic situation is unfavorable for drug treatment. However, an initial reduction in cell numbers produced by surgery, radiotherapy, or cell cycle–nonspecific drugs (alkylating agents, doxorubicin [Adriamycin]) stimulates the slowly dividing cells into more rapid cell division where they become increasingly susceptible to therapy with cell cycle–specific agents (methotrexate, cytosine arabinoside, bleomycin). Thus, an initially slowly responding tumor may actually become more responsive to therapy with continued treatment. The fractional cell kill may actually increase with sequential courses of treatment.

On the other hand, the fractional cell kill hypothesis must be modified in a negative sense to take into account the biochemical heterogeneity of human tumors, an unfavorable property with respect to treatment response. Isoenzyme typing of tumor cells has indicated that most human tumors studied thus far have evolved from a single clone of malignant cells.[3] However, newly developed techniques for *in vitro* cloning of solid tumors have shown this original homogeneity does not persist during later stages of tumor growth. It has been clearly demonstrated that both experimental and human tumors are composed of cell types with differing biochemical, morphologic, and drug-response characteristics.[4] This heterogeneity likely results from somatic mutation of the original tumor line and probably accounts for outgrowth of resistant tumor cells during relapse of formerly sensitive tumors. When subjected to the selective pressure of drug treatment, sensitive tumor cells are destroyed, but the subpopulation of resistant cells survives and proliferates. This process of selecting out resistant cells has been amply demonstrated in cell culture as well as *in vivo*.[5] Thus, cell kill tends to decrease with subsequent courses of treatment, as resistant cell types are selected out, and single-agent treatment is rarely curative. With the possible exceptions of (1) treatment of gestational choriocarcinoma with metho-

trexate and (2) cyclophosphamide treatment of Burkitt's lymphoma, single-agent chemotherapy has not produced longterm survival or cure of advanced malignancies. The most successful drug treatment regimens have combined two or more agents, each of which has a different mechanism of action and each of which has antitumor activity when used individually.

Prediction of Drug Response

The selection of drugs for treating specific diseases is based largely on past experience as reflected in the results of previous clinical trials. However, it would be desirable to predict sensitivity for the specific tumor and patient at hand, and thus avoid the needless toxicity of ineffective agents. Various experimental systems have been studied intensively in the hope of their ultimate use for this purpose. Human tumor fragments can be grown in immunologically incompetent mice[6] (athymic, or nude, mice or thymectomized and irradiated mice) or under the renal capsule of mice.[7] Neither of these systems is entirely satisfactory for routine clinical use; certain tumor types, such as breast carcinomas, do not grow reliably in the immunodeprived mice, while the intact immune system of recipient animals in the subcapsular assay causes tumor regression after the first week of growth. Both systems have the advantage of exposing tumor to drug in the intact animal, allowing the test to be conducted in a pharmacokinetic setting relevant to clinical treatment. All systems require technical expertise and extensive animal facilities beyond the scope of most clinical institutions. Finally, neither the immunodeprived mouse nor the subcapsular assay has been validated as a predictor of response in man.

The *in vitro* culture of human tumors in semisolid media poses a more promising means of pretreatment selection of agents. The technique described by Hamburger and Salmon[8] allows reliable culture of human ovarian cancers, renal cell carcinomas, malignant melanomas, soft tissue sarcomas, and multiple myeloma cells, but less consistent growth of other forms of malignancy. Predictive tests for drug sensitivity are performed by preliminary incubation of a single cell suspension with a range of drug concentrations; after one hour the drug is removed and cells are plated in the semisolid medium. A retrospective analysis of *in vitro* sensitivity and treatment results in 66 patients with ovarian carcinoma, myeloma, and melanoma indicated that the *in vitro* test correctly predicts drug resistance (96 per cent true negative) but has a lower true positive rate of 62 per cent, as only 26 of 42 tumors sensitive *in vitro* responded *in vivo* to the indicated drug.[9] Thus, the assay has considerable value for predicting drug *resistance* for at least these three tumors; it has less value for predicting sensitivity, although the apparent failures may have been due to inadequate drug dosage, pharmacokinetic variability (as discussed below), or other factors that affect drug concentration and duration of exposure in the clinical setting. This assay has some clear disadvantages, including the inconsistent growth of important solid tumors such as breast, lung, and colon carcinoma; the low cloning efficiency of most human tumors (less than 1 per cent); the time required to obtain results (two to three weeks); the problem of testing drugs such as cyclophosphamide, hexamethylmelamine, and procarbazine, which require metabolic activation; and the failure of testing conditions to simulate the drug concentration and duration of exposure that occur *in vivo*. Initial assay conditions were formulated to allow tumor cell exposure to one tenth the maximal drug concentration achieved *in vivo* for one hour, but these conditions are unsuitable for duplicating the *in vivo* cytotoxicity of agents that act in the DNA synthetic phase of the cell cycle. Thus, drugs such as methotrexate and cytosine arabinoside have little effect on cell populations exposed for brief periods; their cytotoxicity is highly dependent on prolonged periods of tumor cell exposure, as revealed in clinical treatment regimens. Even for those tumors that grow in the *in vitro* system, the number of colonies formed is usually less than 50 per plate and thus inadequate to evaluate drug response in one half of tumors tested, and the test system is able to detect cell kill over a narrow range of one log cell kill or less. Despite this long list of limitations, the *in vitro* assay system, with technical improvements, may well become an important aid in choosing antineoplastic therapy.

Biochemical tests based on a knowledge of

the mechanism of action of specific drugs have provided helpful predictions of response in animal tumor systems, but few have been carefully evaluated in man. Test systems have focused on one or several specific determinants, such as the concentration of a key enzyme (deoxycytidine kinase for cytosine arabinoside)[10] or the presence of a specific cytoplasmic receptor (estrogen receptor for estradiol).[11] A few of these tests — most notably, the test for estrogen receptor in breast cancer — have become a cornerstone for making therapeutic decisions; other tests offer considerable promise. The duration of complete remission in acute myelocytic leukemia correlates with the ability of leukemic cells to activate cytosine arabinoside to the active triphosphate form *in vitro*.[12] (Ara-CTP is an inhibitor of DNA synthesis, and is also incorporated into DNA.) High concentrations of alkaline phosphatase, a nucleotide degrading enzyme, are predictive of resistance to 6-mercaptopurine in man.[13] Similarly, high concentrations of dihydrofolate reductase have been associated with resistance to methotrexate.[14] However, these biochemical tests have not been studied prospectively in a sizable patient population to prove their value in routine treatment of leukemia. Each of these examples is considered in greater detail in subsequent chapters.

Pharmacokinetic Determinants of Response

Although the outcome of cancer chemotherapy may depend in large part on the inherent sensitivity of the tumor under treatment, pharmacokinetic factors such as drug absorption, metabolism, and elimination are extremely important in determining the dose, schedule, and route of drug administration. The actual process of planning therapy based on pharmacokinetic considerations is dealt with in Chapter 2.

Pharmacokinetic factors are important not only in protocol design, but also in determining toxicity and response in individual patients. Pharmacokinetics are known to be extremely variable from one patient to the next and may account for the inconsistent responses of tumors that are "sensitive" *in vitro*. Since this interindividual variation is not always predictable on the basis of differences in renal or hepatic function, direct measurement of plasma drug concentrations provides a better guide for dosage adjustment to ensure adequate and safe drug exposure. The interindividual variability in oral absorption of a number of agents, including hexamethylmelamine, methotrexate (in doses over 15 mg/m^2), 5-fluorouracil, and phenylalanine mustard, has been documented by pharmacokinetic studies and must be taken into consideration in planning the route of therapy. In addition, drug monitoring may provide a valuable guide to delayed elimination of agents such as methotrexate, thus allowing early institution of "rescue" procedures[15] and dose adjustment. Reliable assays are available for many antineoplastic agents (Table 1–3); those done by high-pressure liquid chromatography or gas-liquid chromatography require the services of specialized laboratories and usually cannot be performed on a routine basis. A few, such as the competitive binding assays for methotrexate, are available in most cancer treatment centers and have established importance as a guide to the prediction of drug toxicity in high-dose therapy. Principles employed in drug monitoring and their application to cancer treatment are discussed in detail in a subsequent chapter. The utility of various assays is also indicated in the discussion of individual agents.

TABLE 1–3. Drug Assays Useful in Cancer Chemotherapy*

Competitive Protein Binding
Methotrexate
Allopurinol
5-FdUMP (active nucleotide of 5-FU, ftorafur, FUdR)
Radioimmunoassay
Cytosine arabinoside
Bleomycin
? Doxorubicin
Vinca alkaloids
Steroidal agents
High-Pressure Liquid Chromatography
5-FU
Hexamethylmelamine
Phenylalanine mustard
6-Thiopurines
Doxorubicin

*See Pinedo HM (ed.): Clinical Pharmacology of Antineoplastic Drugs. Elsevier/North Holland Biomedical Press, Amsterdam, 1978.

STRATEGIES OF CLINICAL CHEMOTHERAPY

Combination Chemotherapy

Although the first effective drugs for treating cancer were brought to clinical trial in the mid and late 1940s, initial therapeutic results were disappointing. Although impressive regressions of acute lymphocytic leukemia and adult lymphomas were obtained with single agents such as nitrogen mustard, antifolates, corticosteroids, and the vinca alkaloids, responses were only partial and of short duration. When complete remissions were obtained, as in acute lymphocytic leukemia, they were usually less than nine months in duration and relapse was associated with resistance to the original agents used. Attempts at retreatment with new agents usually met with a less satisfactory response or frank resistance to further therapy. Increased doses could not be given because of prohibitive bone marrow or neurotoxicity (vincristine), and few patients derived lasting benefit from single-agent treatment. The introduction of cyclic combination chemotherapy for acute lymphocytic leukemia of childhood in the early 1960s marked a turning point in the effective treatment of neoplastic disease; such combinations are now a standard component of most treatment strategies for advanced cancer.

The superior results of combination chemotherapy as compared with single-agent treatment derive from the following considerations. First, initial resistance to any given single agent is frequent, even in the most responsive tumors; for example, in patients with Hodgkin's disease, the response rate to alkylating agents or procarbazine (the most active single drugs) does not exceed 50 per cent. Second, initially responsive tumors rapidly acquire resistance after drug exposure, probably owing either to selection of pre-existing resistant tumor cells from a heterogeneous tumor cell population (as mentioned previously) or to actual drug induction of resistance. The use of multiple agents, each with cytotoxic activity in the disease under consideration, but with different mechanisms of action, allows for independent cell killing by each agent. Cells resistant to one agent might still be sensitive to the other drugs in the regimen. Third, if these drugs also have non-overlapping toxicities, each can be used in full dosage and the effectiveness of each agent will be maintained in the combination. Drugs such as vincristine, prednisone, bleomycin, hexamethylmelamine, L-asparaginase, and others that lack bone marrow toxicity are particularly valuable for combination with traditional myelosuppressive agents. Based on these principles, curative combinations have been devised for diseases that were not curable with single-agent treatment, including acute lymphocytic leukemia (vincristine-prednisone ± doxorubicin and L-asparaginase), Hodgkin's disease (MOPP), histiocytic lymphoma (C-MOPP), and testicular carcinoma (bleomycin-vinblastine-*cis*-dichlorodiammineplatinum [*cis*-DDP]).

The detailed scheduling of drugs in these combinations was initially based on both practical and theoretical considerations. Intermittent cycles of treatment were used to allow for periods of recovery of host bone marrow and immune function. This strategy allowed for retreatment with full therapeutic doses as frequently as possible in keeping with the fractional cell kill hypothesis. It seems most reasonable to initiate therapy with cell cycle–nonspecific drugs such as the alkylating agents or nitrosoureas (if active against the disease in question) in order to reduce tumor bulk and recruit slowly dividing cells into active DNA synthesis. This phase of cytoreduction can then be followed within the same cycle of treatment by cell cycle–dependent agents such as methotrexate or the fluoropyrimidines. An example of a regimen in which cycle–nonspecific drugs are followed by cycle–specific agents is shown in Table 1–4. More recent combinations have incorporated nonmyelosuppressive agents such as bleomycin, vincristine, prednisone, or high-dose methotrexate with leucovorin rescue in the "off-period" between doses of myelotoxic drugs, in order to provide continuous suppression of tumor growth. High-dose methotrexate with leucovorin rescue has proved to be particularly useful in this capacity in the "off-period" because of its minimal effect on white blood cell and platelet counts.

Cytokinetic considerations also influence the specific scheduling of drug combinations. S-phase (DNA synthetic phase)–specific drugs, such as cytosine arabinoside and methotrexate, tend to block cells during the period of DNA synthesis. Repeat courses of these agents are most effective if administered during the period of rapid recovery of

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