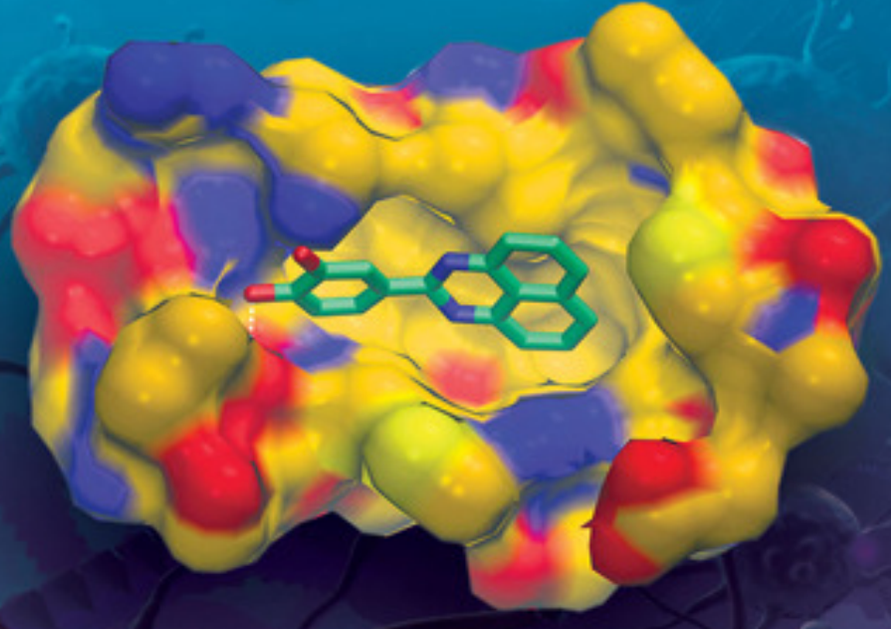
Cancer Chemotherapy, Immunotherapy and Biotherapy

SIXTH EDITION

Principles and Practice



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Wolters Kluwer

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Principles and Practice

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PREFACE

All substances are poisonous; there is none that is not a poison. The right dose differentiates a poison from a remedy.

—PARACELSUS (1538 AD)

For physicians who care for patients with cancer daily, Paracelsus was clairvoyant. Cancer therapy has developed its set of expectations: seriously toxic measures, often without positive results, but undertaken in the hope of averting a potentially fatal outcome. Stem cell transplantation probably represents the epitome of this state of affairs, but, with the exception of hormonal therapies, most cancer treatments fulfilled this forbidding description. However, remarkable progress in the past few years has significantly broadened the therapeutic landscape and improved the outlook for patients with advanced disease. We particularly take notice of the development of new and less toxic targeted therapies, the use of predictive molecular tests for response to treatment, the potential for long-term benefit for patients with advanced disease who are candidates for immune therapies, and continued progress in supportive and palliative care.

Research in both the public and private sectors has added new tools, both drugs and biological compounds, and new biomarkers and diagnostic tests. There is a growing appreciation that not all tumors with the same histological appearance share a common genetic origin. Genomic testing is allowing physicians to select the right treatment for patients with lung, melanoma, thyroid, breast, and many other tumors, contributing to improved survival in patients with the most common forms of malignancy.

Advances that affect patient survival are clear. Adjuvant therapy reduces recurrence rates in node-positive colon cancer and breast cancer by 40%, and the quality of adjuvant therapy is improving with combinations of drugs and biologicals in the earliest stages of disease. The adjuvant use of immunotherapies is now a reality in melanoma and in lung cancer, and neoadjuvant applications are also burgeoning. While this is clear progress, it remains disappointing that in many instances patients are treated with therapies that produce toxic effects but no antitumor effects. Gene arrays that convey useful prognostic information have become common tools for assessing the need for adjuvant therapy in breast cancer, but at present, we lack biomarkers to guide chemotherapy. A further challenge is the need to identify patients with node-negative breast, colon, lung, bladder, and other cancers who have residual disease after primary surgery. Will circulating tumor DNA or circulating tumor cell assays allow us to identify these high-risk patients?

Agents with improved design based on studies of drug resistance to first-line agents are demonstrating better activity in many clinical settings. Third-generation drugs, such as osimertinib and alectinib, that evade resistance mechanisms are improving the treatment of epidermal growth factor receptor (EGFR) or ALK-mutant lung cancers. The principle of expecting improvements in established therapies applies to common agents such as 5-fluorouracil, where alternative fluoropyrimidines (TAS 102, S-1) have achieved success.

The field of antiangiogenic drugs has shown promise for enhancing therapy for solid tumors. Improved small molecules, such as cabozantinib, have yielded significantly better results in clear cell carcinoma of the kidney as compared to earlier antiangiogenic drugs. Significant benefit has accrued from advances in hormonal therapy with receptor degrading molecules and inhibitors of adrenal steroid biosynthesis.

Novel targets of drug action have led to surprising results with novel agents, including the CDK4/6 inhibitors in breast cancer and the PARP inhibitors in breast and ovarian cancer, and the IDH1 and 2 inhibitors in acute leukemia. Discovery of the mechanism of action of the IMiD class of compounds should open new fields of drug development targeting the ubiquitin ligases and associated proteins.

Most impressive has been the rapid evolution of immunotherapies in the past 5 years, as checkpoint antibodies and CAR-T cell therapies enter clinical practice. Much work needs to be done to make these expensive and at times dangerous therapies less toxic and more selective. The challenge of understanding their mechanism of action, developing suitable biomarkers to guide patient selection, and averting serious toxicity remains an unsolved problem, but their benefits cannot be ignored.

This brief but impressive list of advances in the past 5 years indicates not only the quickening pace of new cancer treatments,

but the changing nature of the enterprise. The emphasis now is on developing agents that block key targets in tumor growth, with limited effects on normal tissues. Integration of these new therapies with traditional chemotherapy and with other targeted drugs will require well-planned, biomarker-driven trials. The task ahead of us is daunting. With each new agent acting by a distinct mechanism, the number of potential combinations of agents increases factorially.

In planning the new edition of this book, we have sought to provide the wisdom of experts. The facts contained herein can form a framework from which clinical decisions can be made. However, the facts are not a substitute for excellent clinical judgment. While adherence to protocols is critical, the practice of oncology cannot appropriately be reduced to recipes and algorithms that are universally applicable to every patient. Each physician must develop a sense of what the agents can and cannot do and apply that knowledge to the individual patient, who becomes the host for these foreign molecules. We hope the information in this book can be a useful guide in the development of clinical skills that subsequent experience will embellish and refine.

ACKNOWLEDGMENTS

The sixth edition of *Cancer Chemotherapy, Immunotherapy, and Biotherapy: Principles and Practice* was a labor of love. The last five editions were published by Lippincott Williams & Wilkins, which was acquired by Wolters Kluwer. We were guided by Tim Rinehart, Editorial Coordinator at Wolters Kluwer, who was helpful at every turn. The distinguished roster of contributors wrote remarkably up-to-date chapters and were patient with the iterative process of making requested revisions in a timely fashion. Their motivation to educate the reader about the rapidly changing cancer treatment landscape drove the project to fruition. And lastly, our colleagues have been the inspiration for this book, as they show us how to employ these agents in increasingly effective ways.

The editors are also grateful for having been able to watch and contribute to the development of the field of cancer treatment from its earliest days of exploration of single alkylating agent activity, radical surgery, and localized radiation therapy to the amazing expansion in the number of available tools. Radical surgery, the first curative intervention, is largely being replaced by more limited operations often performed robotically. Technology has continuously improved the capacity to deliver radiation to various tumors with increasing focus and specificity. The improvements in surgery and radiation therapy have led to a closer interdigitation of these treatments with chemotherapy and biological therapies in earlier phases of disease, making a knowledge of pharmacology of even greater importance to multidisciplinary care. The burgeoning of effective drug classes aiming at an increasing number of targets has steadily improved response rates and survival and, somewhat paradoxically, has complicated the process of developmental therapeutics given that we are still quite naive about how to combine agents that interfere with distinct (or even overlapping) targets to achieve optimal anticancer effects at acceptable levels of toxicity. The field of immunotherapy is also beginning to deliver on its enormous promise after years of modest results. We experienced the disappointment when the much-hyped interferon was introduced to enormous fanfare but produced only modest successes in a few rare tumor types and settings at a cost of often intolerable toxicity. However, persistence and accumulating new knowledge is paying off as immune interventions are now achieving long-term disease control in advanced solid tumors that were formerly universally fatal. Antibodies, naked and armed with drugs and radionuclides, cytokines, and adoptive cellular therapies are now essential tools for physicians treating patients with cancer. And the advances are not only helping cancer patients. Therapies such as rituximab and technologies such as bone marrow transplantation, initially developed for cancer, are improving the lives of patients with nonmalignant autoimmune or inherited diseases.

We have moved from the initial successes of single agent (choriocarcinoma) and combination chemotherapy (lymphoma, adjuvant therapy) and are now seeing the emerging successes of myriad novel rational interventions. It is extremely gratifying to have witnessed the change from the revolutionary findings of first our mentors, then our colleagues, and now our mentees. We dedicate this book to all of them in the hope that something between these covers stimulates a thought that leads to something new.

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Section I

Basic Principles of Cancer Treatment

CHAPTER

1

Clinical Strategies for Cancer Treatment: The Role of Drugs

Bruce A. Chabner and Adam C. Palmer

Cancer treatment requires the cooperative efforts of multiple medical specialties. Although surgeons are often the first specialists to treat the cancer patient, the radiation oncologist and medical oncologist have become increasingly important in the initial management of cancer patients, and responsibility for care of patients with metastatic cancer is usually in their hands. The array of alternatives for the treatment of cancer is constantly expanding. As new drugs and new biologics demonstrate effectiveness in advanced disease, and with the evolution of strategies for integrated multimodality treatment, the development of an initial plan of treatment requires the combined input of specialists from pertinent disciplines. The plan must be based on a thorough understanding of the potential benefit and likely acute and delayed toxicities of each component of the treatment regimen, as well as their possible positive and negative interactions.

As a general rule, the medical oncologist is urged to use standard regimens as described in the *Physician Data Query (PDQ)* system of the National Cancer Institute (NCI) (https://www.cancer.gov/publications/pdq). *PDQ* contains information on state-of-the-art treatments for each pathologic type of cancer, as well as a listing of experimental protocols for each disease. A separate list of recommended therapies for different stages and presentations of cancer is offered by the expert panels of the National Cancer Center Network (https://www.nccn.org/professionals/physician_gls/f_guidelines.asp). An important alternative to "standard" therapy is the clinical trial, which should be considered for every eligible patient. Such trials are listed in cancer center and cooperative group websites, and on" Clinical Trials.gov". Trials offer new and potentially more effective treatments for specific subsets of cancer. While response rates have historically been less than 5% in phase I trials of chemotherapy drugs, much higher response and disease control rates have been achieved in genomically selected subsets of lung and other cancers in trials of molecularly targeted drugs, leading to drug approval even after phase I.[1] With either choice, standard therapy or a clinical trial, the medical oncologist and the patient must understand the potential benefits and risks of new and established drugs or combinations of drugs, often integrated with surgery and irradiation. Steps in the decision-making process are discussed to provide the reader with an understanding of strategies for drug treatment of cancer.

Determinants of Treatment Planning

The first and primary determinant of treatment is the histologic diagnosis. Malignant neoplasms occur in many different pathologic forms, each with a characteristic natural history, pattern of progression, and responsiveness to treatment. Thus, the *histologic diagnosis*, usually made by biopsy or excision of a primary tumor, is of critical importance as a first step in treatment planning. The clinical oncologist must be alert to the possibility of atypical presentations of treatable and even curable tumors, such as germ cell tumors of the testis, lymphomas, and breast cancer, and must ask for special immunohistologic or molecular tests to rule in or rule out a potentially curable tumor type.

In a growing number of cases—for example, lung carcinoma or the non-Hodgkin's lymphomas—accurate pathological and molecular *subtyping* of tumors is important because the subtypes of these diseases have different natural histories and responses to treatment. Genomic analysis may be necessary for further delineation and more effective therapy of subsets of the lung, colon, melanoma, gastric, and esophageal cancer but may be complicated by the intratumoral heterogeneity of molecular subclones.[2]

Mutant forms of the epidermal growth factor receptor (EGFR), ALK, and ROS-1 identify unique subgroup of patients with non–small cell lung cancer highly responsive to targeted drugs, while the absence of *KRAS* mutation in colorectal cancers implies a reasonable chance of response to the anti-EGFR receptor antibodies, cetuximab, and panitumumab.[3] In breast cancer, the status of estrogen or progesterone receptors and amplification of the *HER*-2 oncogene guide the decision to use hormonal therapy or adjuvant chemotherapy, with an anti-Her2 antibody, and influence the selection of specific drugs or regimens. Predictors for response and benefit for checkpoint inhibitors include microsatellite instability in colorectal cancer and other microsatellite unstable tumors,[4] and the status of beta-2-microglubulin expression, and PDL-1 expression in non–small cell lung cancer.[5] These and other molecular and immunohistochemical tests are indispensable in making appropriate therapeutic decisions. Molecular profiling of tumors will contribute more significantly in the future, as targeted molecules gain a greater foothold in cancer treatment.

Staging

Following the precise workup of pathological samples, the next step in treatment planning is to determine the clinical extent of disease and specifically to determine whether the tumor is curable by local treatment or requires systemic treatment. This *staging* process requires radiological studies and biopsies of suspicious lesions. The treatment of Hodgkin's lymphomas, while primarily based upon combination chemotherapy, will require radiation therapy if a large mediastinal mass is present and does not regress completely on PET scanning. Patients with disease confined to a single lymph node site or area (stage I) are curable with a limited number of cycles of reduced intensity chemotherapy, while more advanced stages (II to IV) must be treated with aggressive chemotherapy regimens. Further, in planning treatment for apparently localized breast cancer, the choice of modalities for definitive therapy may vary depending on the size of the primary tumor, the presence of cancer at the margins of resection or the involvement of lymph nodes. Similarly, the need for adjuvant chemotherapy for breast and colorectal cancers and adenocarcinoma of the lung will depend on, among other factors, whether regional lymph nodes are involved with tumor.

For metastatic cancer, the number and locations of metastases may require multiple interventions such as resection of a solitary lung or brain lesion or radiation therapy to a site of potentially dangerous vertebral or hip metastasis, in addition to systemic chemotherapy. Thus, accurate determination of the location and extent of disease is critical to the planning of initial therapy.

Individualizing Treatment Choice

An additional factor, the patient's probable tolerance for the side effects of the various possible treatments, must also be considered. Not all cancer patients are suitable candidates for intensive treatment. Severely debilitated patients and those with underlying comorbid problems—for example, heart disease, renal or hepatic dysfunction, advanced diabetes, neurological impairment, or chronic obstructive pulmonary disease—might well suffer severely disabling or fatal complications from the side effects of a potentially curative regimen. Common drugs such as cisplatin, doxorubicin, and methotrexate can have devastating side effects if used in the wrong patient. The physician may have to reduce doses in cases of organ dysfunction or choose a less toxic, palliative regimen. The ultimate decision to use drugs must be based on a comprehensive understanding of the disease and the patient in question, the *clinical* pharmacology of drugs, and the potential benefits and risks of alternatives, such as radiation therapy, or surgery.

TABLE

1.1 ***Pharmacogenomic tests for cancer chemotherapy***

Genetic Test	Disease	Clinical Impact	Commercial Laboratory (Examples)[a]
Thiopurine methyltransferase[b]	Childhood ALL	Identifies patients at high risk of 6-MP toxicity	ARUP Laboratories (Salt Lake City) (https://www.aruplab.com/oncology/tests) Promethius Laboratories (San Diego); Mayo Clinic (http://mayoresearch.mayo.edu/center-

			for-individualized-medicine/drug-gene-testing.asp)
UDP glucuronyltransferase 1A1[b]	Colorectal cancer	Identifies patients at high risk of irinotecan toxicity	ARUP Laboratories (https://www.aruplab.com/oncology/tests)
Dihydropyrimidine dehydrogenase[b]	Any 5-FU containing regimen	Identifies patients at high risk for 5-FU toxicity	ARUP Laboratories (Salt Lake City) (https://www.aruplab.com/oncology/tests)

[a]Many cancer centers and hospitals offer an array of diagnostic molecular tests.

[b]Test of host DNA for polymorphism.

Pharmacogenomic differences are increasingly identified as influencing response and toxicity of cancer drugs. Polymorphisms of genes responsible for inactivating irinotecan (UGT1A1), 6-mercaptopurine (thiopurine methyltransferase, TMPT), and 5-fluorouracil (5-FU; dihydropyrimidine dehydrogenase, DPD) may be responsible for delayed drug clearance, leading to unexpected toxicity (see Chapters 5 and 8). Tests for the inherited gene variants are available through genomics companies or specialized laboratories in cancer centers (Table 1.1).

The design of multidrug treatment regimens is based on a number of considerations. These include (a) responsiveness of the pathologic and molecular type of tumor to specific drugs, (b) the biochemical mechanisms of cytotoxicity of each drug, (c) drug cross-resistance patterns, and (d) potential drug interactions affecting pharmacokinetics, toxicity, or response. The molecular actions and pharmacokinetic features of individual drugs are considered in detail in succeeding chapters, but a brief review of the impact of these factors on trial design at this juncture provides a framework for understanding regimen design.

Finally, in the context of information about tumor histology, stage, and molecular features, and with information about the patient's age and baseline health, the oncologist must decide whether a realistic opportunity exists for cure. A decision to treat with curative intent demands a high degree of adherence to drug dosage and schedule, as specified in the standard or experimental regimen, and a willingness to accept treatment-related toxicity. When cure is not a realistic expectation, treatment decisions are based on an expectation for prolonging life or improving the quality of life through relief of pain or disability. In patients receiving purely palliative treatment, dosage adjustments or treatment delays help to minimize the impact of myelosuppression or mucositis but at the cost of antitumor efficacy.

The Various Roles of Drug Therapies in Cancer Treatment

Following the diagnostic workup and initial surgical biopsy or excision of tumor, multiple treatment options are available to the team of physicians who treat cancer (Table 1.2).

Among these options, drugs (including chemotherapy, targeted agents, and immunotherapies) may be used with or without irradiation, depending on the tumor presentation, sites of disease, and specific kind of cancer. Although initially developed for treatment of patients with metastatic cancers, drugs are now routinely used before or after the primary surgical excision of tumor. Cytotoxic drugs cure some disseminated cancers and are effective in decreasing tumor volume, alleviating symptoms, and prolonging life in many forms of metastatic cancer, even those that are not curable. *Adjuvant* therapy regimens are used in patients who have had primary tumors resected and who, although possibly cured by surgery, are at significant risk of recurrence. Adjuvant therapy decreases tumor recurrence rates and prolongs survival in patients with breast cancer, colorectal cancer, non–small cell lung cancer, osteosarcoma, and other tumors. *Neoadjuvant* drug therapy effectively reduces the bulk of locally extensive tumors *prior to* initial surgical resection, allowing less destructive and more effective resection. Neoadjuvant therapy with drugs or hormonal agents is often used with or without irradiation in patients with locally advanced breast cancer; head and neck, bladder, esophageal, prostate, and non–small cell lung cancer; osteosarcoma; and soft tissue sarcomas. This approach potentially preserves the breast and reduces the extent of surgery for the bladder, anus, head and neck, and other sites of cancers. In the treatment of osteogenic sarcoma, the clinical response of the tumor mass to chemotherapy, prior to resection, can serve as an indication of

tumor sensitivity to the drugs used and therefore a signal to continue chemotherapy after surgery.

TABLE

1.2 ***Options for treating cancer***

Modality		Example Disease	Example Treatment
1.	**Surgery**		
	Removal of primary tumor	Breast cancer	Lumpectomy or mastectomy
	Reduction of tumor volume	Ovarian cancer	Debulking of intra-abdominal disease
	Resection of solitary metastasis	Soft tissue sarcoma with isolated lung metastasis	Resection of lung lesion
	Biopsy of metastasis	Non–small cell lung cancer	Provide tissue for molecular analysis
2.	Radiation therapy		
	Curative therapy for local disease	Hodgkin disease, stage 1	Regional lymph node irradiation
	Local control of primary tumor, cure unlikely	Locally advanced cervical cancer	Pelvic irradiation
	Combined irradiation and chemotherapy for local control and potential cure	Locally advanced head and neck cancer	Irradiation to tumor and regional lymph nodes, with concurrent cisplatin
	Postsurgical treatment to prevent local disease recurrence	Breast cancer with lymph node involvement	Irradiation to chest wall and axillary lymph nodes
	Palliative treatment of metastatic lesion to prevent serious complication	Breast cancer	Irradiation to brain, spinal cord, or hip lesion
3.	**Chemotherapy**		
	Curative treatment of systemic disease	Hodgkin disease	ABVD chemotherapy
	Adjuvant chemotherapy	Breast cancer, hormone and HER-2 receptor negative, stage I–II	Adriamycin, cyclophosphamide, taxane
	Palliative treatment of metastatic cancer	Colon cancer, stage IV	FOLFOX chemotherapy
	Regional chemotherapy	Meningeal leukemia	Intrathecal methotrexate
4.	Targeted molecular therapy		
	Treatment of metastatic disease	Non–small cell lung cancer	Erlotinib for EGFR-mutated lung cancer, stage IV
	Adjuvant therapy, with chemotherapy	Breast cancer, stage I-II, HER-2 positive	Trastuzumab with paclitaxel
5.	**Immunotherapy**		
	Palliative treatment of metastatic disease	Melanoma, stage IV	Anti-PD1 antibody
	Adjuvant therapy	Melanoma, stage III	Anti-PD1 antibody

Kinetic Basis of Drug Therapy

The objective of cancer treatment is to reduce the tumor cell population to zero. Chemotherapy experiments with rapidly growing transplanted leukemias in mice established the validity of the *fractional cell kill hypothesis*, as developed by Skipper et al.,[6] which states that a given drug concentration applied for a defined time period will kill a constant fraction of the tumor population, independent of the absolute number of cells. Regrowth of tumor occurs during the drug-free interval between cycles of treatment. Thus, each treatment cycle kills a specific fraction of the remaining cells. Assuming that drug-resistant cells do not outgrow, the results of treatment are a function of (a) the dose of drug administered, (b) the fraction of tumor cells killed with each treatment, and (c) the number and frequency of repetitions of treatment. Based on these cytokinetic considerations, most chemotherapy regimens from the 1950s to 1990s consisted of 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 was to reduce the absolute number of remaining tumor cells to 0 (or <1) through the multiplicative effect of successive fractional cell kills (e.g., given 99% cell kill per cycle, a tumor burden of 10^{11} cells will be reduced to <1 cell with six cycles of treatment: $[10^{11}\text{ cells}] \times [0.01]^6 < 1$).

Regimens of intensive, cyclic chemotherapy, based on the fractional cell kill hypothesis, were successfully implemented to cure human leukemia and lymphoma. These regimens combined multiple active drugs selected for nonoverlapping toxicities, in order to maximize the tolerable combined dose, and therefore the extent of cell kill per cycle. This approach was less successful in treating the more slowly growing and clonally diverse solid tumors in humans. It is now realized that a number of confounding factors alter the fundamental assumption of a constant fractional cell kill per treatment cycle (see Fig. 1.1, The Cell Cycle).

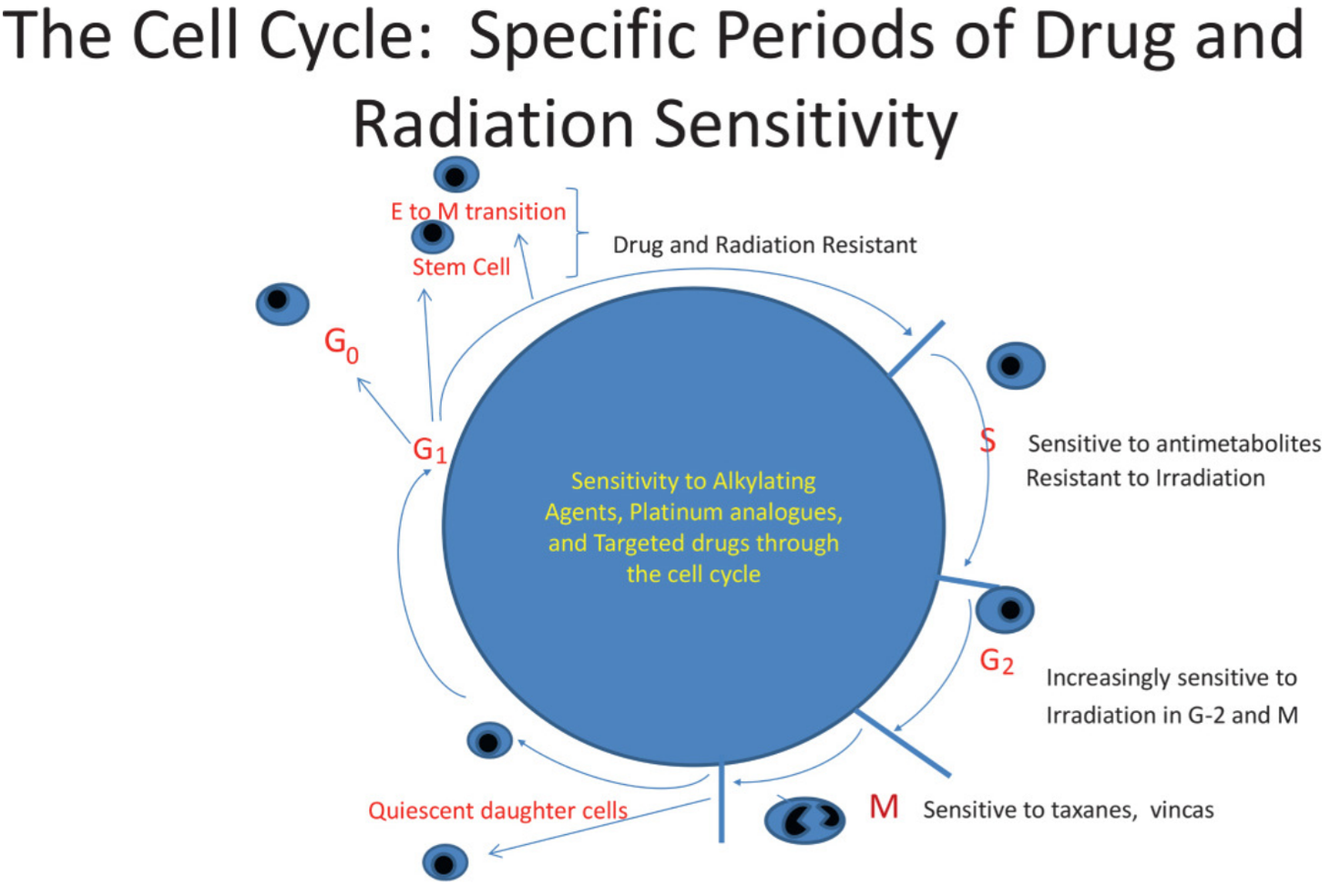

FIGURE **1.1** The figure illustrates the different phases of the growth cycle of tumor cells. G_1 is the phase of cell growth prior to the DNA replication (S). Cells are most vulnerable to antimetabolites damage during S-phase. Cells enter an interphase (G_2) prior to actual cell division in M, or mitotic, phase. A small subpopulations of nondividing, or slowly dividing cells, may be generated during mitosis (quiescent cells and stem cell like G-0 cells). These cells are less vulnerable to cancer treatment and may re-enter active proliferation, depending on oxygenation, perfusion, or other growth stimuli. The relative sensitivity of common treatment modalities for each of these phases of the cell cycle is indicated. Oncogene regulation, p53 status and responses to DNA damage may also influence drug and radiation sensitivity of normal and malignant cells. (From Comaills V, Kabeche L, Morris R, et al. Genomic instability is induced by persistent proliferation of cells undergoing epithelial-to-mesenchymal transition. *Cell Rep*. 2016;17:2632-2647.)

The assumptions that a uniform cell growth rate and uniform drug sensitivity characterized all cells in a given tumor were incorrect. Many solid tumors (such as lung and colon cancers) become clinically apparent at a stage of decelerating growth, when tumor vascularity is not uniform and not adequate to provide oxygen and nutrients to the bulk of the tumor, leading to nonuniformity of growth rate. These large tumors contain a significant fraction of slowly dividing or noncycling cells (termed "G_0 cells") (Fig. 1.1). Since most antineoplastic agents, particularly the antimetabolites and antitumor antibiotics, are most effective against rapidly dividing cells, cell killing will not be uniform throughout the tumor. Some drugs selectively kill cells during specific phases of the cell cycle (S-phase, for cytosine arabinoside, and mitosis, for the vincas and taxanes) and depend on there being a rapid rate of cell division. Others are most active during other brief phases in the cell cycle, as for example, radiation therapy in G-2, the interphase between DNA synthesis and mitosis or the taxanes and vinca alkaloids during mitosis (M phase). The initial kinetic features of cells in a large, poorly vascularized, and slowly growing tumor are unfavorable for treatment with cell-cycle phase-specific drugs.[7] To address this heterogeneity, alkylators and adduct-forming platinum derivatives, which attack DNA in all phases of the cell cycle, are used in combination with antimetabolites such as 5-FU and pemetrexed and antimitotic drugs such as the taxanes. An initial reduction in cell numbers produced by surgery, radiotherapy, or non–cell-cycle-specific drugs may improve blood flow (and drug delivery) and thereby push the slowly dividing cells into a state of more rapid cell division, where they become increasingly susceptible to therapy with cell-cycle-specific agents. Fractional cell kill may actually increase with sequential courses of treatment, as in the treatment of bulky tumors, such as testicular cancers and lymphomas, that are cured by chemotherapy.

Assumptions that a tumor population is biologically uniform are inaccurate.[8] The clonal evolution and molecular diversity of any given population of tumor cells, all derived from a common founder cell, have now been amply demonstrated in human tumors. That diversity encompasses not only the emergence of unique *driver mutations* in subsets of tumor, but a diversity of *mutations that confer drug resistance* may be found in subpopulations in a single site of tumor, and in multiple different metastatic sites. When a diverse population of tumor cells is subjected to the selective pressure of drug treatment, drug-sensitive tumor cells are destroyed, but subpopulations of resistant cells survive and proliferate. With some notable exceptions (treatment of chronic myelogenous leukemia [CML] with imatinib, gestational choriocarcinoma treated with methotrexate, cyclophosphamide treatment for African Burkitt's lymphoma, and cladribine treatment for hairy cell leukemia), single-agent therapy rarely produces long-term remission or cure of advanced malignancies. The diversity of resistance mechanisms and secondary driver mutations has been demonstrated in solid tumors and leukemias following treatment with molecularly targeted agents.[9]

An additional flaw in the kinetic theory, and a reason for failure of cyclic combination chemotherapy, is the existence of stem cell populations within the tumor; these nondividing cells possess a multidrug-resistant and radiation-resistant phenotype and may lie dormant for years.[10] They possess the capacity of unlimited self-renewal when awakened by unknown stimuli. The origin of these stem cells is uncertain. The process of cell division, while assigning equal complements of DNA to each daughter, consistently generates a small population of nondividing or quiescent cells, impervious to treatment, but capable of resuming cell-cycle progression.[11] Thus, the failure of therapy may result from the persistence of quiescent and relatively drug-resistant cells after eradication of the more drug-sensitive and actively dividing bulk of tumor.

Selection of Therapy Based on Molecular Profiling: Precision Medicine

Clinical trials have set the standard for treatment of most types of cancer, but for most metastatic cancers, only a fraction of patients respond to chemotherapy, and those responses are temporary and incomplete. To avoid the needless toxicity of ineffective treatment, especially in diseases with only modest rates of response, it would be desirable to predict sensitivity for the specific tumor and patient at hand. Various systems have been established to predict response to chemotherapy and some even commercialized for testing tumor cells in vitro, but only fragmentary evidence, and no prospective controlled trial data, exists to justify their routine use. However, with the advent of routine genomic profiling of many histological categories of human cancer, treatments are increasingly based on the idea of matching the drug to the tumor genomics in an approach often called Precision Medicine.

The strategy of patient selection based on molecular biomarkers has proven to be a powerful tool in the development of molecularly targeted drugs. These agents are designed to block the biochemical function of driver mutations, to which certain tumors are addicted; inhibiting these drivers lead to cell death. The first successful use of biomarkers to select patients was

employed for hormonal therapy in breast cancer treatment (estrogen and progesterone receptor). With the discovery of specific molecular changes (mutations, translocations, amplifications) that drive human cancers, drug development changed course in the late 1990s. The first of many targeted therapies was directed against the *bcr-abl* tyrosine kinase that underlies CML. Imatinib, an inhibitor of the kinase, introduced in 2001, proved to have striking activity in the chronic phase of CML and has limited toxicity for normal bone marrow cells.[12] Because imatinib also inhibits the c-kit tyrosine kinase, it is effective against gastrointestinal stromal tumors (GIST). Most patients with GIST express a mutated and activated form of the *c-kit* receptor. Pretreatment sequencing of the *C-KIT* gene provides important prognostic information and allows appropriate selection of patients for treatment with imatinib (exon 11 mutations), sunitinib (exon 9 mutations), or other experimental drugs.[13]

The strategy was successful applied to the use of drugs that block the HER-2-amplified kinase in breast cancer, C-KIT in GIST, the tyrosine kinases that drive melanoma, non–small cell lung cancer, and thyroid cancer, and other molecular subsets of cancer (see relevant chapters). Selection of patients for specific targeted therapies, based on molecular biomarkers, has dramatically improved response rates in early drug trials, leading to approvals for marketing after phase II or even after phase I for 10 to 20 new targeted agents yearly in the time period from 2010 to 2017, in contrast to the 1 to 4 new agents approved each year for cancer in the chemotherapy era.

The list of molecularly targeted agents, discussed in various chapters of this book, is constantly growing. Effective agents target the oncoproteins produced by the *EML4-ALK* mutation in non–small cell lung cancer, the *RET* mutation in medullary thyroid cancer, and the polyadenosyl ribose phosphatase (PARP) DNA repair function in breast and ovarian cancer.[14] Monoclonal antibodies (trastuzumab and cetuximab) are proving most effective when used in combination with cytotoxic agents. These results give hope that in the future, cancer treatment will be much more grounded in individualized treatment selection based on tumor genomics.

With rapid approval of new targeted agents, oncologists must undertake genomic profiling for both common and rare tumors and must be able to interpret molecular findings in these reports in their choice of drugs. Genomic profiling is not only useful in choosing the initial therapy. Repeat tumor biopsies at the time of tumor progression or monitoring of circulating tumor DNA in plasma are undertaken for characterization of drug resistance and for choosing the next therapy, as drugs specific for certain resistance mutations (osimertinib for T790M in EGFR-mutated lung cancer, and ponatinib for the highly drug-resistant mutation [T315I] in CML) come into practice. A cogent example of clonal evolution during therapy was provided by studies of prostate cancer, which usually presents as a modestly mutated primary tumor. In contrast, multiple different mutations are found after androgen deprivation therapy in castration-resistant disease, in which a diversity of mechanisms are found, often in a single patient: PTEN loss or activation of AKT (promoting tumor survival), androgen receptor mutations, and receptor splice mutations or amplification, all leading to antiandrogen resistance.[15] Each of these changes would call for a different choice of next therapy (Chapter 28).

It is important to realize the limitations of precision medicine. The drugs are costly, have idiosyncratic and unpredictable toxicities, often inhibit off-target kinases, and as single agents do not address the genomic complexity of many drug-resistant cancers and do not account for the “tissue context” (e.g., BRAF inhibitors in melanoma versus colon cancer) that may determine response versus resistance.[16] Nonetheless, genomic profiling and patient selection are clearly a step forward toward rational cancer therapy.

Pharmacokinetic Determinants of Response

Although the outcome of cancer treatment depends in large part on the inherent sensitivity of the tumor being treated, the chances for success can be compromised by the oncologist’s failure to consider important pharmacokinetic factors such as drug absorption, metabolism, elimination, and drug interactions in designing experimental regimens and in clinical practice.

The pharmacokinetics of a given schedule of administration are subject to significant interindividual variability in drug concentration over time (see Chapter 5). The origin of this variability is multifactorial. Pharmacogenetic variants (polymorphisms in expression of drug-metabolizing enzymes and receptors) determine the rate of elimination and thus the toxicity of some drugs, including irinotecan (glucuronyl transferase UGT 1A1), 6-mercaptopurine (thiopurine methyltransferase), and 5-FU (dihydropyrimidine dehydrogenase). In addition, variability in hepatic microsomal isoenzyme activity, serum albumin levels that affect protein binding of drug, and age-related changes in renal tubular function all contribute to variability of drug clearance and

drug toxicity in elderly patients. As a result, in a patient population with apparently normal renal and hepatic function, measurement of drug levels in plasma will reveal at least a three- to fourfold variability around the mean drug concentration at any given time point and an equal interindividual variability in drug exposure, expressed as the area under the drug concentration in plasma (times) time curve (AUC) for a given dose of drug.

Pharmacokinetic factors are important not only in general protocol design but also in determining specific modifications of dosage in individual patients. Dosage may be increased or decreased empirically, based on observed patterns of toxicity (neutrophil count following cytotoxic drug, acneform rash after EGFR inhibitor therapy). Drug levels are routinely measured in only a few settings, as for example, to identify patients at high risk of toxicity in high-dose methotrexate and to adjust dosage to achieve optimal blood levels in children receiving methotrexate for acute lymphocytic leukemia (ALL) (see Chapter 7). Response rates improve and episodes of extreme toxicity are unusual when 5-FU drug levels are monitored and doses adjusted to reach prespecified pharmacokinetic end points.[17] However, monitoring of 5-FU drug levels is not accepted as a routine practice.

Most drugs are cleared through hepatic metabolism or renal excretion. Renal or hepatic dysfunction may delay drug elimination and result in overwhelming toxicity (see Chapter 4). To avoid such toxicity, doses of certain agents must be modified based on estimates of renal or hepatic function, as will be discussed in the individual drug chapters.

Rationale for Combination Therapy

Although the first effective drugs for treating cancer were brought to clinical trial in the late 1940s, initial therapeutic results were disappointing. As single agents, methotrexate and nitrogen mustard caused impressive regressions of ALL and adult lymphomas, respectively, but responses were of short duration, and relapse was invariably associated with resistance to further treatment by the same agent. Both historically with cytotoxic chemotherapy, and presently with targeted therapies, with rare exceptions resistance to a given single agent emerges eventually if not quickly, even for the most responsive tumors. In patients with Hodgkin's disease, for example, the complete response rate to alkylating agents or procarbazine does not exceed 20%, and virtually all patients relapse within weeks or months. Studies of imatinib resistance in CML have verified the long-standing hypothesis that untreated tumors harbor spontaneously resistant cells, which are selected and emerge clinically following drug exposure. Additionally, anticancer drugs and radiation therapy increase the rate of mutation to resistance in experimental studies, as does hypoxia.[18] Experiments with human solid tumors suggest that a subset of tumor cells, probably harboring either genetic or epigenetic features that promote survival, may persist after treatment and may spontaneously give rise to drug-resistant clones.[10]

The first motivation proposed for combination therapy was to address the heterogeneity of drug response found within a single tumor (which we call intratumor heterogeneity) and the selection for drug-resistant cells during treatment; application of combination therapy to the cancer problem was inspired by the success of multidrug regimens to cure tuberculosis infections. The use of multiple agents, each with cytotoxic activity in the disease under consideration but with different mechanisms of action, allows independent cell killing by each agent and discourages the outgrowth of malignant clones resistant to any single agent. If the frequency of resistance to one drug is low, and a second drug (or third drug and so on) lacks cross-resistance to the first agent, then the frequency of simultaneous resistance in any single cell to all agents shrinks rapidly with an increasing number of active drugs that lack cross-resistance. The success of this approach was demonstrated by cyclic combination chemotherapy ("total therapy") for ALL of childhood in the early 1960s,[19] which marked a turning point in the effective treatment of neoplastic disease.

The heterogeneity of response to chemotherapeutic agents found among a cohort of patients with tumors of a given histological type (intertumor heterogeneity) is a second motivation for combination therapy, the need for which became evident early in the history of combination therapy.[20,21] The chances of establishing remission for a population of patients harboring genetically diverse tumors, all of the same histological type, meant that increasing the number of agents, each with a different mechanism of action, was required to produce maximal numbers of responses. The benefit achieved can be represented as the sum of independent drug action, in which the remission rate depends on the probabilities that either drug alone induces remission (see Figs. 1.2 and 1.3). Put simply, two chances for remission are superior to one, although this depends on the drugs not sharing cross-resistance. The first cures for ALL demonstrated that combination therapy is an effective approach in addressing both inter- and intratumor heterogeneity, because more patients respond and also their responses are categorically superior. In childhood ALL combining two or three chemotherapies increased the rate of remission (as in Fig. 1.2), combining four or five chemotherapies produced cures in a minority of patients, and combinations of up to eight different drugs made cures commonplace (Fig. 1.4).[20]

Variability in drug response across patient populations is a near-ubiquitous feature of cancer treatment, and for this reason, managing intertumor heterogeneity remains a challenge and an important rationale for combination therapy.

The question arises as to whether the benefits of combination therapy reflect actual drug synergy: a greater effect than would be expected from the sum of the independent actions of the drugs rather than simply additive benefit. While synergy may apply in specific regimens, many successful combinations achieve an observed result that equals the expected effect of *independent* drug action; as shown in Figure 1.3, improvements in the average survival of a patient population can be explained without imposing the idea that drug combinations are synergistic in each individual patient.[23] But it is also possible for multiple active drugs to deliver enhanced control of individual tumors. Here the notion of *independent* drug action applies in a different way: if two cancer killing drugs are not cross-resistant, then cells have statistically independent chances of being killed by either drug. Statistically, independent drug action means that the log-kills achieved by each drug in a combination will simply add up: for example, if each of two drugs can alone kill 90% of cancer cells (1 log-kill per drug), their independent combined effect is to kill 99% of cancer cells (2 log-kills). Note that when measuring the fractional killing of cancer cells, *drug independence* therefore has the same meaning as *drug additivity* (this is not generally true in other domains of pharmacology). Synergistic interaction between the effects of multiple drugs can further enhance response to treatment, but it is not necessary to invoke synergy to achieve a clinically beneficial combination therapy.

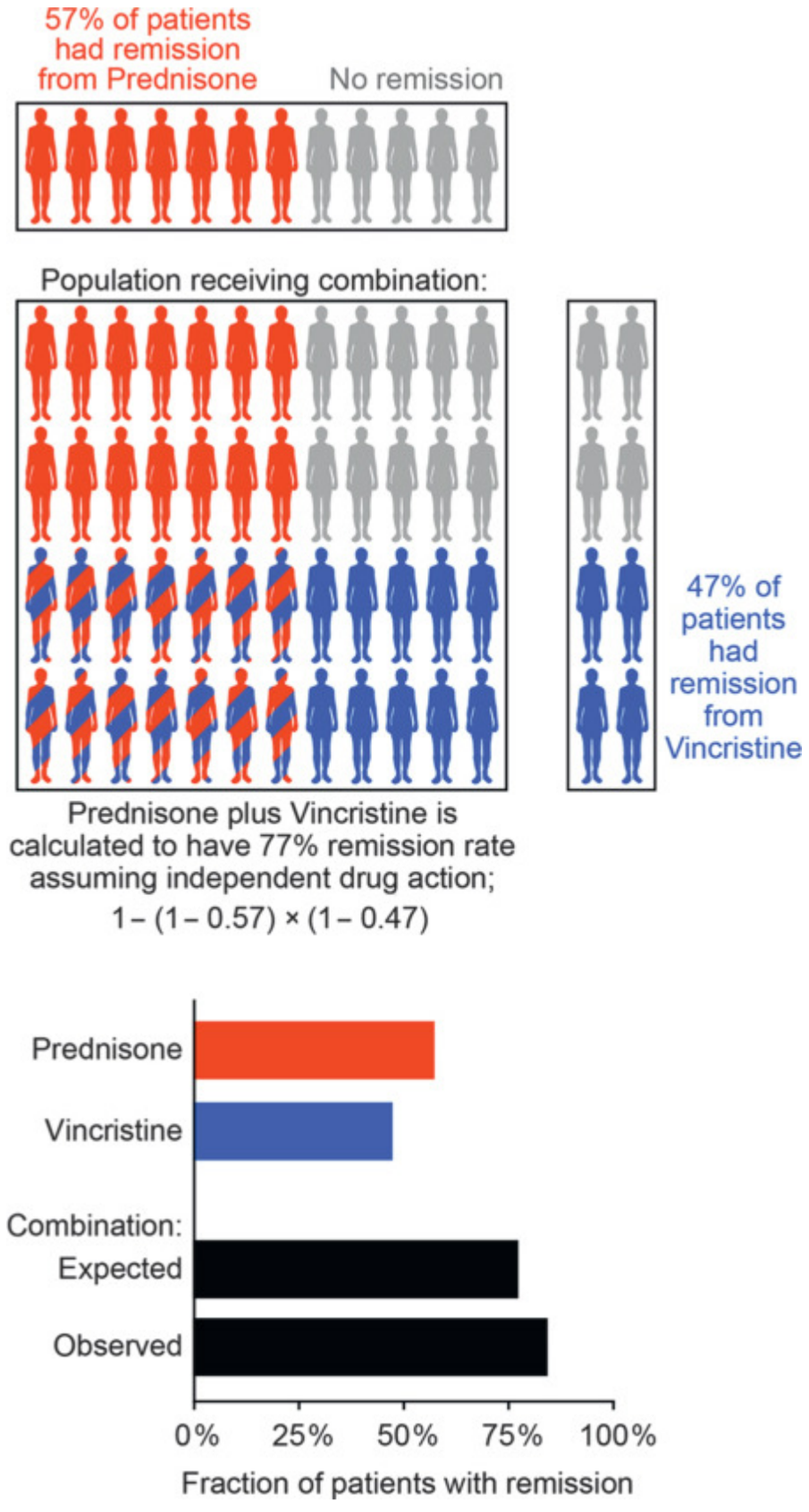

FIGURE **1.2** The benefit of independent drug combinations. In childhood acute lymphocytic leukemia, early trials of single-drug treatments showed that prednisone induces remission in 57% of patients, and vincristine induces remission in 47% of patients. Frei III et al. surmised that if the drugs act independently, then the combination of both drugs should have a remission rate of 77% [1 − (1 − 0.57) × (1 − 0.47)]; this proved similar to the observed rate of 84%. Independent drug action, calculated in this manner, accurately described the superior remission rates of a number of different combination regimens. (From Frei E III. The effectiveness of combinations of antileukemic agents in inducing and maintaining remission in children with acute leukemia. *Blood*. 1965;26:641-656; Palmer AC, Sorger PK. Combination cancer therapy can confer benefit via patient-to-patient variability without

drug additivity or synergy. *Cell.* 2017;171:1678-1691.e13.)

As discussed, patterns of cross-resistance must be taken into consideration in formulating drug combinations. Cross-resistance between drugs affects the capacity of drug combinations to manage both intratumor and intertumor heterogeneity. Resistance to many agents may result from unique and specific mutations or amplifications, for example, as may occur in the genes coding for enzymes or receptors inhibited by antimetabolites (such as dihydrofolate reductase or thymidylate synthase) or the mutant tyrosine kinases blocked by molecularly targeted drugs (BCR-ABL, EGFR, EML4-ALK).[24] Drug resistance mutations affecting cell survival pathways, such as the bcl-2 or PI-3 Kinase cascades, or multidrug resistance transporters may lead to broad cross-resistance (see Table 1.3).

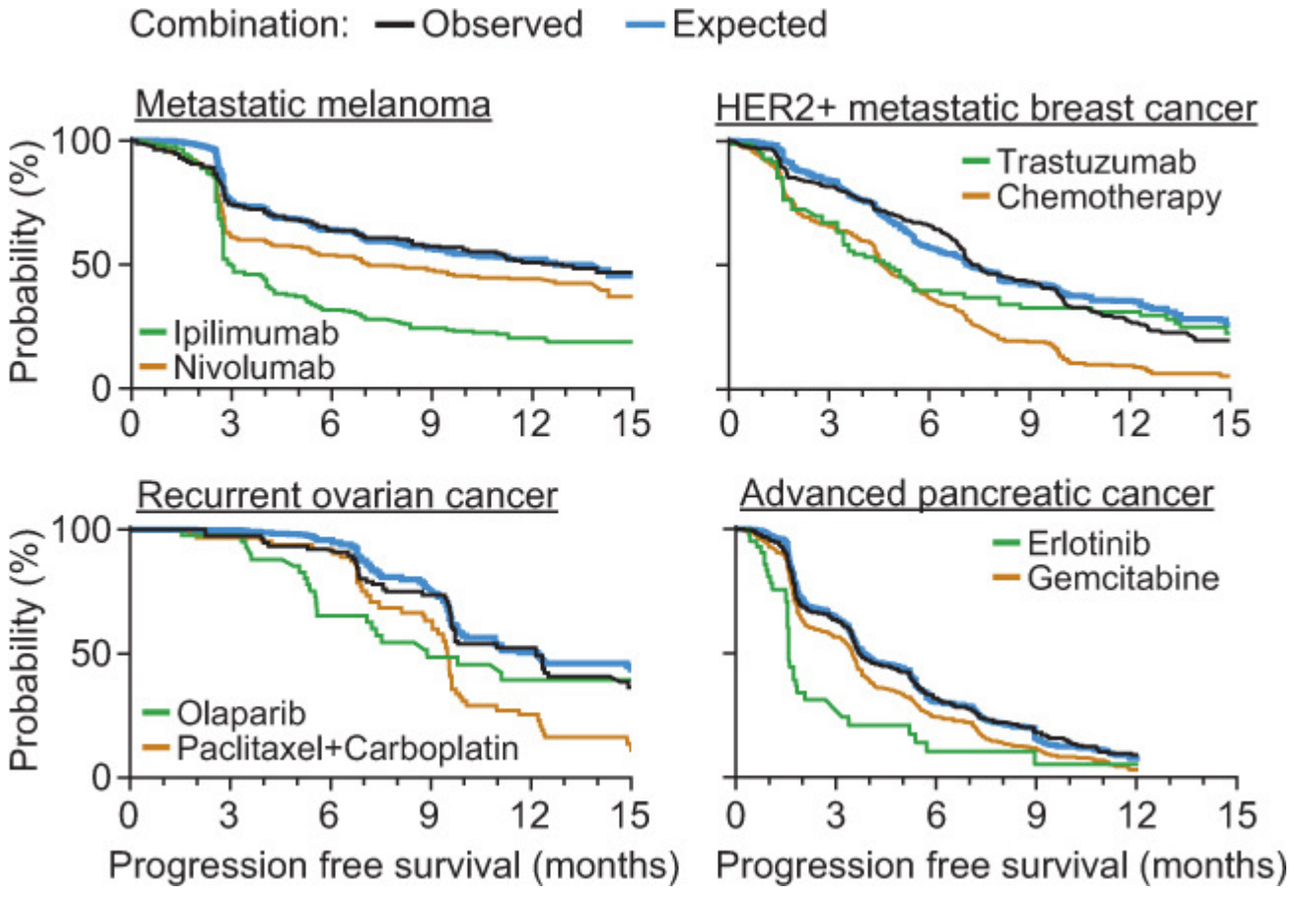

FIGURE **1.3** Longer progression-free survival from independent drug combinations. When two or more active drugs are combined, which each individually confer some probability of durable progression-free survival, then their combination may be expected to further increase the probability of progression-free survival, provided that the drugs are not cross-resistant. This demonstrates that drug combinations do not need to act synergistically to meaningfully improve patient survival, although if synergy occurs it can further improve benefit. (From Palmer AC, Sorger PK. Combination cancer therapy can confer benefit via patient-to-patient variability without drug additivity or synergy. *Cell.* 2017;171:1678-1691.e13.)

The most thoroughly studied and undoubtedly one of the more important mechanisms of multidrug resistance is increased expression of the *MDR-1* gene[25] and its gene product, the P-glycoprotein (*pgp*). This gene codes for *pgp*, which promotes the efflux of vinca alkaloids, anthracyclines, taxanes, actinomycin D, epipodophyllotoxins, other natural products, and even small molecules that target tyrosine kinases. This protein occurs constitutively in many normal tissues, including most stem cells, and mature epithelial cells of the kidney, colon, and adrenal gland and has been identified in tumors derived from these tissues. It is prominently expressed in many tumors recurring after chemotherapy, including lymphomas, myeloid leukemias, multiple myeloma, and other cancers. *Pgp*-mediated resistance, and the associated decrease in intracellular drug levels, can be reversed experimentally by calcium-channel blockers, various steroid hormones, and cyclosporine analogues. Results of clinical trials investigating the use of agents to reverse multidrug resistance have been confounded by pharmacokinetic interactions, increased toxicity, and inconclusive therapeutic results.

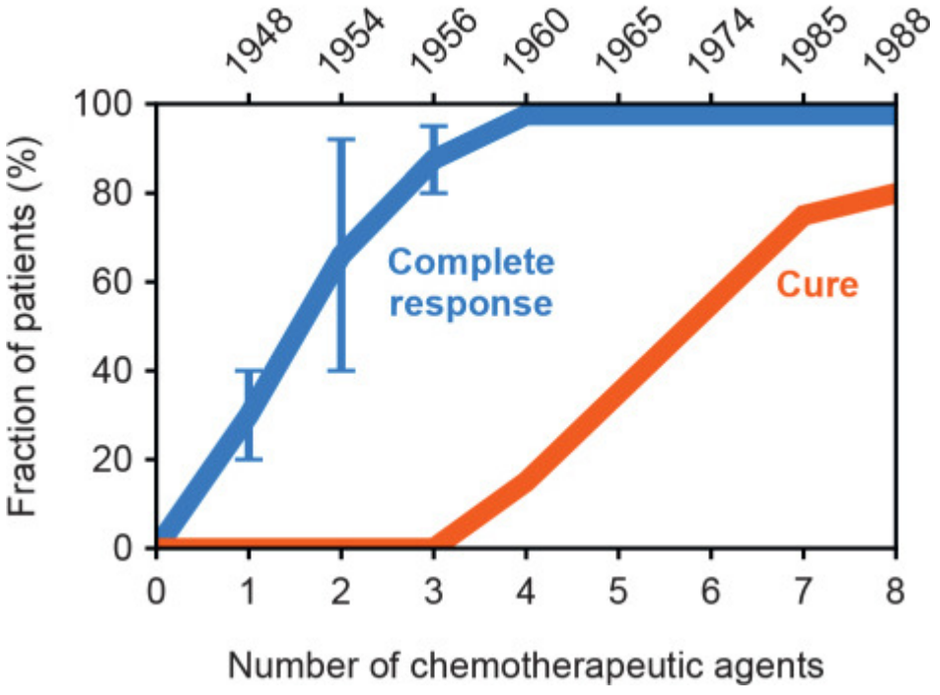

FIGURE **1.4** Combination chemotherapy is essential to curing childhood acute lymphoblastic leukemia. Early combinations of small numbers of chemotherapeutic agents produced a higher rate of complete remission, and subsequent development of combinations of larger numbers of agents produced cures with increasing frequency. Chemotherapeutics were introduced in the sequence: methotrexate, 6-mercaptopurine, prednisone, vincristine, intrathecal methotrexate, adriamycin, asparaginase, ara-C. (From Frei E III. Studies of sequential and combination antimetabolite therapy in acute leukemia: 6-mercaptopurine and methotrexate. *Blood.* 1961;18:431-454; Frei E III. The effectiveness of combinations of antileukemic agents in inducing and maintaining remission in children with acute leukemia. *Blood.* 1965;26:641-656; Eder JP, et al. Principles of dose, schedule and combination chemotherapy. In: Hong WK, Holland JR, Frei E III, eds. *Cancer Medicine*. 8th ed. People's Medical Publishing House; 2016.)

A second class of efflux transporters, the multidrug-resistance proteins (MRPs), may also confer complex patterns of cross-resistance. In experimental tumors, these efflux pumps promote drug efflux and confer resistance to anthracyclines, etoposide, taxanes, and vinca alkaloids, as well as many of the targeted small molecules. Members of the MRP family may also mediate efflux of methotrexate, 6-mercaptopurine, and camptothecin derivatives.[25] The MRP family of genes is widely expressed in epithelial tumors, and their potential for mediating multiagent resistance deserves further study.

Finally, classic alkylating agents (cyclophosphamide, melphalan hydrochloride, nitrogen mustard) may share cross-resistance related to enhanced DNA repair or by increased intracellular nucleophilic thiols, such as glutathione. Increased expression of nucleotide excision repair (NER) components correlates with a poor outcome in ovarian cancer (ERCC1) and in bladder cancer (ERCC2) treated with platinum-based regimens.[26] Not all alkylating agents share cross-resistance. As mentioned earlier, resistance to the nitrosourea, procarbazine, dacarbazine, and other methylating alkylators is mediated by increased levels of a different enzyme, methyl guanine methyl transferase, which removes the adduct from purine bases in DNA (Chapter 12).

DNA repair defects may have either synergistic interactions or may confer resistance to therapy. Increased expression of NER components mediates resistance to bischloroethyl alkylators. Alternatively, defective mismatch repair (MMR) is associated with a high number of genomic mutations and *increases the response rate to* checkpoint inhibitors in colon cancer treatment. Alternatively, an MMR complex recognizes areas of altered DNA duplex pairing and activates apoptosis and is required for sensitivity to methylating drugs and platinating agents. A single mutation in one component of this system, such as *MSH6*, *confers resistance* to platinating drugs and methylating agents, as well as 6-mercaptopurine.[27]

TABLE

1.3 ***Mechanisms of resistance to cancer drug treatment chemotherapy***

Mechanism of Resistance	Drug	Alteration

Decreased drug uptake	Methotrexate sodium	Decreased expression of the folate transporter
Decreased drug activation	Cytosine arabinoside, fludarabine, cladribine Methotrexate	Decreased deoxycytidine kinase Decreased folylpolyglutamyl synthetase
Increased drug target	Methotrexate 5-Fluorouracil	Amplified DHFR Amplified TS
Absent or mutated drug target	Etoposide Doxorubicin	Altered topo II
Enhanced DNA repair	Alkylating agents, platinum analogs Nitrosoureas, procarbazine, temozolomide	Increased nucleotide excision repair Increased O^{6M}-alkyl-guanine alkyl transferase
Defective recognition of DNA adducts	Cisplatin, 6-mercaptopurine	Mismatch repair defect
Increased drug efflux	Doxorubicin, etoposide, vinca alkaloids, paclitaxel, topotecan	Increased MDR expression or MDR gene amplification
Defective checkpoint function and apoptosis	Most anticancer drugs	*p53* mutations, bcl2 activation or overexpression
Molecularly Targeted Drugs		
Mutation of target	Most tyrosine kinase inhibitors: for example, EGFR inhibitors Imatinib, nilotinib, dasatinib	 T790M in EGFR T315 I in BCR- ABL
Activation of an alternative pathway	EGFR inhibitors BRAF inhibitors PIK3CA kinase Inhibitor	c-MET amplification RAS family mutation Activation of AKT, loss of PTEN
Hormonal Therapies		
Mutation of target	Androgen receptor Estrogen receptor	Mutation prevents binding of antagonist
Amplification of target	Androgen receptor Estrogen receptor	Increased target prevents shut down of pathway
Splice variants	Androgen receptor Estrogen receptor	Ligand-independent signaling maintains pathway
Activation of cell survival pathway	PTEN loss, PI3Kinase mutation	PI3Kinase pathway activation promotes cell survival

DHFR, dihydrofolate reductase; MDR, multidrug resistance; topo II, topoisomerase II; TS, thymidylate synthase; EGFR, epidermal growth factor receptor.

Multiple different mechanisms of resistance can be detected in tumor cells in a single patient. Inherited polymorphisms may contribute to resistance. Hormonal therapies are affected by mutations that alter splice splicing of the androgen or estrogen receptor, leading to constitutive receptor activation in the absence of ligand; hormonal therapy resistance can also result from receptor amplification or mutation, all of which can be detected in circulating tumor cells or circulating tumor DNA in single patients who display resistance to therapy[26,28] (see Chapters 27 and 28).

The introduction of monoclonal antibodies for cancer treatment has led to the successful use of trastuzumab with taxanes for breast cancer, rituximab with various chemotherapies for lymphoid tumors, bevacizumab with 5-flurouracil and oxaliplatin for colon cancer, and cetuximab (erbitux) with irinotecan for colon cancer (Chapter 29). This success is attributed to several mechanisms: (a) the ability of bevacizumab to normalize blood flow and improve cytotoxic drug delivery to otherwise poorly

perfused tumors; (b) the proapoptotic effects of receptor inhibitors such as trastuzumab and cetuximab, which block the antiapoptotic signaling from mutated, overexpressed, or amplified tyrosine kinases; and (c) invocation of immune mechanisms (cell mediated or complement mediated) of cell death by antibodies (Chapter 29). Unfortunately, targeted small molecules have exhibited less synergy than have antibodies in combination with chemotherapy. Small molecular weight inhibitors of EGFR and VEGFR have not enhanced the efficacy of chemotherapy in the lung and breast cancer. The reasons for the greater effectiveness of monoclonal antibodies in combination therapy may relate to their additional ability to mobilize the immune response, such as complement-mediated cytotoxicity or T cell–mediated effects. Trials of checkpoint inhibitor antibodies with chemotherapy are showing promising results for lung cancer and Hodgkin's disease,[29] in spite of the immunosuppressive effects of chemotherapy.

A further step in rational therapy will be the use of multiple targeted agents in rational combinations to block parallel pathways that account for resistance to single agents. Laboratory experiments with human tumor cells in culture suggest that synergistic combinations of targeted drugs can be identified for many lung cancer patients, but limited evidence has been presented for this strategy in improving patient outcomes.[30] To date, the most successful example is the combination of a BRAF inhibitor with a MEK inhibitor for melanoma (see Chapter 22). However, effective implementation of a strategy for combination therapies will depend on accurate genomic profiling of tumor prior to therapy and early introduction of a second agent when genomic evidence of resistance is detected in the bloodstream. Circulating tumor DNA may reveal the necessary information without invasive biopsy.[9] This issue of combining multiple targeted agents is more fully discussed in Chapters 21 and 22.

Schedule Development in Combination Therapy: Kinetic and Toxicity Considerations

The detailed scheduling of drugs in multidrug regimens is based on both practical and theoretical considerations. Intermittent cycles of treatment permit periods of recovery for host bone marrow, gastrointestinal tract, and immune function, with the expectation that recovery of the tumor cell population would be slower than that of the injured normal tissues. A commonly used strategy in designing chemotherapy regimens is to incorporate myelotoxic agents on day 1 of each cycle, while delivering nonmyelosuppressive agents, such as bleomycin, vincristine, prednisone, or high-dose methotrexate with leucovorin rescue, during the period of bone marrow suppression (e.g., on day 8 of a 21-day cycle) to provide continuous inhibition of tumor growth while allowing maximum time for marrow recovery. Effective interdigitation of immunotherapy with cytotoxic or targeted therapies, or with radiation therapy, is still in development. It is unclear whether the suppressive therapies are optimally effective if used prior to, with, or after checkpoint inhibitors. Drugs or radiation have the potential of suppressing the systemic immune response to immunotherapies, and destroying T-cells that are infiltrating a tumor. On the other hand, cytotoxic treatment that releases tumor antigens might enhance immune recognition. Further studies are needed to determine if chemotherapy, targeted drugs, or radiotherapy can be used either concurrently or sequentially with checkpoint therapy without compromising the latter although early studies with combined checkpoint anti-PD1 and chemotherapy show positive results in lung cancer.[31]

Although most of the common anticancer drugs are administered as bolus infusions, continuous infusions provide longer exposure to chemotherapy above the threshold for cytotoxicity and may improve or change the toxicity profile for normal tissues. The R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) regimen, in which chemotherapy drugs are given as a 96-hour infusion, has produced impressive rates of response and long-term disease free survival in greater than 90% of AIDS-associated Burkitt's lymphoma and in other high-grade lymphomas. Infusional regimens cause less nausea, vomiting, bone marrow suppression, and cardiotoxicity as compared to bolus regimens (R-CHOP).[32] Extended infusion regimens have improved therapeutic ratios, decreasing bone marrow toxicity and increasing response rates for 5-FU when given as a multiday infusions rather than in a bolus dose.[33] The continuous infusion of a cell-cycle-phase–specific agent such as cytosine arabinoside or 5-FU allows a greater fraction of the tumor cell population to be exposed to drug during the sensitive S-phase of the cell cycle, as compared to the more limited exposure after intermittent bolus therapy. The same prolongation of exposure can be achieved by designing prodrugs that are slowly metabolized to the active parent, as accomplished by capecitabine, an orally administered fluoropyrimidine, or by changing the formulation of the drug, as with liposomal encapsulation of doxorubicin and cytosine arabinoside.[34]

Additional Considerations in Combination Chemotherapy: Taking Advantage of Mutations in DNA Repair and Apoptosis

Mutations in DNA repair pathways predispose to malignancy. These repair processes and the common lesions that impair their function in cancer are shown in Table 1.4.

Drug discovery efforts are aimed at taking advantage of these alterations in repair or apoptosis. For example, double-strand breaks in DNA are repaired through homologous recombination, a process that requires BRCA1 and BRCA2. Alkylating agents, anthracyclines, and platinum analogues cause double-strand DNA breaks and show strong activity against BRCA1- or BRCA2-mutant tumors.[35] BRCA1- and BRCA2-mutant breast cancer and prostate cancer lack the capacity to repair double-strand breaks and therefore depend on the PARP enzyme complex to repair single-stranded breaks. If not repaired, these single-strand breaks become double-strand lesions that lead to apoptosis. An inhibitor of PARP-mediated repair of single-strand breaks has significant activity against BRCA1/2-mutant breast and ovarian cancers[14] and BRCA2-deficient prostate cancer.[36] Since many chemotherapeutic agents produce double-strand breaks (alkylating agents, platinating drugs), combining PARP inhibitors with chemotherapy is a logical approach but has been impaired by bone marrow suppression of combinations of olaparib and cisplatin.

Apoptosis is an active, energy-requiring, and protein synthesis–dependent process whereby cells, in response to specific signals, undergo an orderly, programmed series of intracellular events that lead to death. This process is a necessary component of normal development in all multicellular organisms and is required to control the cell population of many normal proliferating or renewable tissues such as the lymphatic and hematopoietic systems. Suppression of apoptosis, as for example, through loss or mutation of p53, is a common feature of neoplastic transformation.[37] It may be the direct result of mutation or overexpression of antiapoptotic genes such as BCL-2 as in lymphomas, or indirectly, through activation of growth factor pathways such as the PI-3 kinase and epidermal growth factor (EGF) pathways in epithelial cancers or through amplification of *HER-2* in breast cancer. Translocation and overexpression of BCL-2 are a hallmark of follicular B-cell lymphomas, but the same gene is commonly overexpressed in epithelial tumors. Activation of other protective factors such as NF-**κ**B and the PI-3 kinase pathway in response to DNA damage suppresses cytotoxicity of chemotherapy drugs and radiation. Lowe et al.[37] elegantly demonstrated that the presence of wild-type *p53* conferred tumor sensitivity to doxorubicin, 5-FU, and etoposide, as well as x-irradiation, while the same cells lacking a functional p53 gene were drug and irradiation resistant. This and other studies link the loss of cell-cycle control to resistance to chemotherapeutic agents and explain the high rate of inherent drug resistance of many p53-mutated solid tumors. Furthermore, these results suggest potential targets for effectively bypassing the elaborate defense machinery available to the cancer cell. Drugs are currently in development that activate apoptosis (TRAIL receptor agonists, MDM inhibitors) or attack antiapoptotic proteins, such as the BH3 domain proteins. Venetoclax, a drug that inhibits the antiapoptotic bcl-2, has been approved for drug-resistant chronic lymphocytic leukemia.[38]

TABLE

1.4 ***DNA repair processes and role in drug sensitivity or resistance (see applicable chapter for reference)***

Repair Process	DNA Lesion Repaired	Example of Drug Sensitivity or Resistance
Polyadenosyl ribose polymerase (PARP)	Signals need for excision and repair of damaged DNA Base	Olaparib inhibits PARP, causes regression of BRCA1- or BRCA2-deficient tumor
Nucleotide excision repair	Excision of alkylated or platinated DNA	Overexpression of ERCC2 in bladder cancer leads to resistance to cisplatin
Homologous recombination	Repair of cross-linked DNA	BRCA1- or BRCA2-deficient tumors are sensitive to cisplatin and olaparib
Methylguanine methyltransferase	Removes alkylated bases	Presence in brain tumors leads to resistance to procarbazine or temozolomide
Mismatch repair	Recognizes alkylated DNA lesions, inducing apoptosis	Loss of mismatch repair component leads to temozolomide resistance

Dose-Intensification Strategies

Dose intensification has received increasing emphasis in recent years as a strategy for overcoming resistance to chemotherapy. The intensity of conventional treatment, that is, the dose per time unit, correlates with decreased recurrence rates in adjuvant therapy of breast cancer.[39] By decreasing the interval between treatments, a "dose-dense" regimen, improves relapse-free survival. Drug-responsive tumors have a steep dose-response curve, thus indicating the importance of delivering maximum tolerated doses as rapidly as possible. The following dosing principles derived from the treatment of Hodgkin's disease are broadly applicable to other curable cancers: (a) Do not modify planned doses or schedules of chemotherapy in anticipation of toxicity that has not yet happened, nor for short-term, non–life-threatening toxicity, such as emesis or mild neuropathy. (b) Because significant individual variation may exist in the pharmacokinetics of drugs or in the sensitivity of the bone marrow (and other normal organs) to drug-related toxicity, the granulocyte count should be used as an in vivo biologic assay of the individual dosage limits of myelotoxic agents. Dose escalation is built into many chemotherapy protocols to achieve a target nadir of 1,000/mm^3.

While readily tolerable ("standard") doses of combination chemotherapy drugs are sufficient for patients with sensitive tumors, greater dose intensity may be necessary for the subset of patients with drug-resistant tumors. The challenge is to identify reliable predictive tumor markers (such as, potentially, bcl-2 overexpression in large cell lymphoma or mutations in p53 or K-RAS genes) or pharmacokinetic parameters that identify patients who will benefit from more intensive therapy. In the absence of such markers, the only alternative is to treat every potentially curable patient with maximally tolerated doses, as established by the published or experimental protocol. An alternative strategy for dose intensification is to shorten the interval between courses, as has been done in dose-dense breast cancer chemotherapy.[39]

Recombinant hematopoietic growth factors can mitigate the bone marrow toxicity of chemotherapy. Granulocyte colony-stimulating factor is effective in decreasing the duration of granulocyte nadir after myelotoxic chemotherapy. However, erythropoietin preparations decrease survival in some settings and should only be used to correct chemotherapy induced anemia with Hg < 10 g/mm^3 in symptomatic patients (see Chapter 34).

High-Dose Chemotherapy

Marrow-ablative dosages of chemotherapy represent the ultimate extrapolation of the dose intensity concept. In practice, it is possible to rescue the host with either autologous bone marrow or peripheral blood stem cells or with stem cells or marrow from an allogeneic but histocompatible donor. During the past 45 years, marrow-ablative chemotherapy with stem cell rescue has become standard as salvage therapy for patients relapsing after primary treatment for leukemias, Hodgkin's and non-Hodgkin's lymphomas, multiple myeloma, other hematologic malignancies, and testicular cancers. Marrow from a human leukocyte antigen (HLA)-compatible donor has the advantage of being free of malignant cells and contains T lymphocytes that generate a strong, and potentially curative, graft versus tumor response. The drugs and doses used in these programs would otherwise cause fatal myelosuppression as their primary dose-limiting toxicity, but with marrow transplantation, extramedullary toxicities become limiting. Alkylators such as busulfan, ifosfamide, and cyclophosphamide are prominent in most ablative regimens because characteristically their extramyeloid toxicity becomes dose limiting only at multiples of their standard dosage. *High-dose regimens exaggerate the extramyeloid toxicities of each drug and introduce new sites of organ damage*. Virtually every organ in the body, including the heart, lungs, liver, gastrointestinal epithelium, and the nervous system, may suffer significant acute and/or chronic toxicity during or after high-dose chemotherapy, and the specific patterns of such toxicity and their reversibility are discussed in relevant chapters.

Randomized trials comparing high-dose regimens with best conventional therapy generally have not proven the value of dose escalation in patients with metastatic solid tumors, with the possible exception of relapsed testicular cancer.[40] High-dose regimens with allogeneic bone marrow transplant are curative in approximately 40% to 50% of patients with acute myeloid leukemia, whereas autologous bone marrow or peripheral blood stem cell transplant regimens are equally effective in drug-responsive Hodgkin Disease in first or second relapse and in intermediate-grade and high-grade non-Hodgkin lymphoma in first relapse. One should remember that both the acute and the late toxicities of high-dose chemotherapy in both autologous and allogeneic bone marrow transplant regimens are formidable and may decrease long-term survival due to later development of myelodysplasia, acute myeloid leukemia, and cardiovascular disease.[41] Acute and chronic graft versus host disease, opportunistic infection, acute gastrointestinal and pulmonary toxicity, and venoocclusive disease of the liver result from drug damage to bone marrow, epithelial

tissue, and vascular endothelium, respectively, contribute to mortality of high-dose alkylator regimens.

Drug Interactions in Combination Chemotherapy: Pharmacokinetic Interactions and Overlapping Toxicity

Specific drug interactions, both favorable and unfavorable, must be considered in developing combination regimens. These interactions may take the form of pharmacokinetic, cytokinetic, or biochemical effects of one drug that influences the pharmacokinetic or pharmacodynamic properties of a second component of a combination. Patterns of overlapping toxicity are a primary concern. Drugs that cause renal toxicity, such as cisplatin, must be used cautiously in combination with other agents (such as methotrexate, pemetrexed, the purine analogues, or bleomycin) that depend on renal elimination as a primary mechanism of excretion. It is particularly important to monitor renal function in regimens that incorporate cisplatin with pemetrexed or etoposide, as dose adjustment of the second agent may be necessary to avoid toxicity. Paclitaxel delays the clearance of doxorubicin and increases the risk of cardiotoxicity.[42]

Overlapping toxicities are a primary impediment to some combinations. Trastuzumab and doxorubicin cause incremental cardiac toxicity. Induction of microsomal metabolism by phenytoin or phenobarbital accelerates the clearance of irinotecan, paclitaxel, vincristine, and imatinib. Most “targeted” drugs are cleared by microsomal metabolism and may be ineffective when used with an inducer (see Chapter 21), omeprazole, rifampin, statins, ritonavir, or adrenal steroids. The opposite effect, a diminished clearance of the cancer drugs, results from their combined use with cytochrome inhibitors, such as ketoconazole. The potential for important interactions between cancer drugs and other medications must always be kept in mind during the routine care of cancer patients, who are often receiving concurrent antibiotics and other agents.

Biochemical interactions between cancer drugs also may be important considerations in determining the choice of agents and their sequence of administration. Both synergistic and antagonistic interactions have been described. A cancer drug may be modulated by a second agent that has no antitumor activity in its own right, but that enhances the intracellular activation or target binding of the primary agent or inhibits the repair of lesions produced by the primary drug. An example of this synergy is the use of leucovorin (5-formyl tetrahydrofolate), which itself has no cytotoxic effect but which, when converted to the active cofactor N-5,10-methylene-tetrahydrofolic acid, enhances the binding of 5-FU to its target, thymidylate synthase, forming a ternary complex with enzyme and 5-dFUMP (see Chapter 8).

Combined Chemotherapy and Radiotherapy

A further innovation in the use of antineoplastic drugs is to combine drugs with irradiation to take advantage of the well-documented synergy between irradiation and cisplatin, 5-fluorouracil, paclitaxel, or cetuximab. Gemcitabine, a most potent sensitizer to irradiation, must be used at fractional doses with irradiation. The mechanism of synergy for each drug is discussed in detail in specific chapters.

The design of integrated chemotherapy-radiotherapy combinations presents special problems because of the synergistic therapeutic, and toxic, effects of the two therapies on both normal and malignant tissue. The normal tissue of greatest concern is the bone marrow, although intestinal epithelium, heart, lungs, brain and any other organ in the path of the beam may be affected. Radiation given to the pelvic or midline abdominal areas produces a decline in blood counts, and a decrease in bone marrow reserve. This can severely compromise the ability to deliver myelotoxic chemotherapy, even months or years after the radiation. Conformal irradiation narrows the irradiation field and preserves a greater portion of the marrow-bearing tissue. For some toxicities, the sequence of administration of drugs and irradiation may be crucial. For example, mediastinal irradiation after combination chemotherapy for massive mediastinal Hodgkin’s disease has proven to be practicable and effective. Because the initial chemotherapy results in significant shrinkage of the mediastinal tumor, smaller radiation portals can be used to encompass the residual tumor with proportionately less radiation damage to lungs and heart. Concurrent irradiation and chemotherapy is superior to radiotherapy alone in adjuvant therapy for head and neck cancer (with cisplatin and 5-FU),[43] anal cancer (with mitomycin or 5-FU),[44] cervical cancer (with cisplatin),[45] and rectal cancer (with 5-FU).[46] Thus, although it is important to consider the cumulative toxicities of chemotherapy and radiation on bone marrow and other vulnerable tissues in the radiation field, the therapeutic benefits of simultaneous irradiation and chemotherapy often outweigh the disadvantages.

Many chemotherapeutic agents greatly potentiate the effects of irradiation and may lead to unacceptable toxicity for organs

usually resistant to radiation damage. Doxorubicin sensitizes both normal and malignant cells to radiation damage, possibly because both doxorubicin and x-rays produce free-radical damage to tissues. Doxorubicin adjuvant chemotherapy given in conjunction with irradiation to the left chest wall increases the risk of intense skin reactions and cardiac toxicity in patients with left breast cancer.[47] Extreme care must be taken in treatment planning to the dose of irradiation to the heart. Bleomycin and gemcitabine strongly enhance the toxicity of irradiation.

Chemotherapy and irradiation are both carcinogenic. In patients treated with both modalities and cured of Hodgkin disease, the risk for secondary solid tumors in the irradiation field, including breast cancers and sarcomas, increases to approximately 15% at 15 years and 20% at 25 years.[48] The most important chemotherapy-related second malignancy is leukemia due to DNA alkylating or methylating agents. Among the most potently leukemogenic agents are the mustard-type alkylators, nitrosoureas, and procarbazine. A qualitatively different type of secondary non-lymphocytic leukemia is associated with topoisomerase II inhibitors, including etoposide, and doxorubicin (see Chapter 14).[49] Characteristically, acute myelogenous leukemia associated with topoisomerase II inhibitor therapy (anthracyclines or etoposide) has a shorter latency period (1 to 4 years) than does alkylator-induced myelodysplasia and leukemia (3 to 7 years after treatment). Leukemias arising after topo-isomerase inhibitor treatment are often associated with reciprocal translocations involving the *MLL* gene at chromosome band 11q23.

Conclusion

The physician must use her/his intimate knowledge of drug efficacy and toxicity to achieve maximum benefit. The foregoing discussion emphasizes that tumor biology, drug mechanisms, drug disposition, and drug interactions, as well as acute and late side effects, are critical considerations in the design and application of effective cancer chemotherapy. Most recently, research is moving the chemotherapy field very rapidly in the direction of personalizing therapy; the hope is that understanding the biology of each tumor at the molecular level at every step in the treatment continuum will add highly relevant information and improve the specificity of treatment, but it will bring additional complexity to the challenge of selecting appropriate therapy for individual patients. The following chapters present information on individual drugs and, if mastered, will enhance the success of our efforts to treat cancer.

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CHAPTER

2

Target Identification and Drug Discovery

Bruce A. Chabner

This chapter provides an overview of the discovery and preclinical development of small molecules for anticancer treatment. The Reader is referred to Chapters 29 to 32 for in depth discussion of immunotherapies, and for other specialized chapters dealing with hormonal agents and biological molecules.

A Brief History of Cancer Drug Discovery

The history of cancer drug discovery begins with the initial experiments of Goodman and Gilman during and after the second World War[1,2]; they showed that alkylating mustards produced antitumor effects in murine test systems, leading to the first trials of nitrogen mustard against a patient with Hodgkin's disease. Their work and the subsequent establishment of the initial cancer drug development program at the National Cancer Institute (NCI) in 1956 led to the successful identification of other chemotherapeutic drugs in industry and at the NCI, and the incorporation of multiple drugs into curative regimens for leukemia, lymphomas, and testicular cancer.[2] These agents, identified in empirical screening systems that used murine leukemias, were primarily antiproliferative, targeting steps in DNA synthesis or physically interacting with and damaging DNA. They were nonselective in the sense that they were toxic to all proliferating cells, including bone marrow and intestinal epithelium, and for poorly understood reasons, had a positive therapeutic index: the injury to normal tissues was reversible, while some tumors were completely eradicated. For these early drug discovery efforts, screening libraries were composed of random chemicals, nucleotide analogues, electrophilic alkylating type analogues, and randomly collected fermentation or plant-derived products. The yield in new drugs rarely exceeded 1 to 2 new active chemical entities approved for human use in any given year. Prior to 1990, screening systems for new drugs consisted primarily of tumor cell lines, first of murine origin (L1210, P388 leukemias) and later, in 1984, a panel of 60 human tumor cell lines.[3] There was no specific molecular target in this strategy, although the cell line panel was developed with the intention, not realized, of finding tumor-specific drugs. In subsequent years, the 60 cell line panel has been extensively characterized with regard to genomics, mechanisms of DNA repair, and drug resistance[4,5] and has become a widely used tool for evaluation of compounds in development against cancer. The screening systems used by NCI yielded a number of very active and ultimately useful products, including taxanes[6] and platinum analogues.[7] The empirical screens proved particularly adept at identifying basic classes of cytotoxic compounds, including antimetabolites, antimitotic drugs, topoisomerase inhibitors, and a variety of unusual natural products, such as taxanes and podophyllotoxins.

A Transition to Targeting "Driver" Mutations

A revolution of cancer drug discovery occurred in the years from 1990 forward, as the result of burgeoning biological understanding of cancer as a disease driven by oncogenic mutations that could be targeted for cancer-specific drug development. The biological basis for the concept of "driver mutations" arose from discoveries in the NCI's viral oncology program. Harold Varmus and Michael Bishop's discovery of the SRC viral oncogene, and its counterpart c-SRC in animal tissues, won a Nobel Prize in 1989 and set in motion a search for similar genes in human tumors.[8] These oncogenic drivers have since been revealed in many different subsets of human tumors through genomic analysis[9] and through reference to a comprehensive genome wide