Chapter 1
Principles of Medical Oncology and Chemotherapy

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Introduction

Advances in chemotherapy, surgery, radiation therapy, and interventional oncology have made cancer treatment an increasingly complex endeavor. Multidisciplinary strategies continue to improve patient outcomes while minimizing toxicity. The role of the medical oncologist is to deliver chemotherapy and coordinate multispecialty treatment for patients diagnosed with cancer. Increasingly, medical oncologists rely on interventional oncologists to deliver targeted treatments for palliation, and at times, long-term survival. In order to optimize collaboration between disciplines, this introductory chapter will provide insight into the process that the medical oncologist undertakes when assessing a patient and planning for his/her treatment. In addition, it will provide an overview of chemotherapy, biologic/targeted therapy, and response to treatment.

Diagnosis and Staging

Human malignancy takes many forms, and the role of chemotherapy in its treatment varies. Intravenous cytotoxic chemotherapy often comprises the entire treatment, with curative intent, in leukemia, lymphoma, and germ-cell tumors such as testicular cancer. In contrast, the majority of potentially curable solid tumors require a multidisciplinary treatment approach in which chemotherapy plays a complementary role to surgery, radiation therapy, and local ablative treatments. Establishing the initial histologic diagnosis is imperative to guide the direction of therapy.

Diagnosis begins with a comprehensive patient history and physical, often followed by baseline radiologic imaging for preliminary staging and to identify the optimal site for obtaining a tissue diagnosis. Immunohistochemistry and genotype analysis play a critical role in establishing the diagnosis and therapy for a cancer, and this often impacts the decision to obtain a core biopsy rather than a fine needle aspirate. Once core biopsy of a lesion is obtained, medical oncologists rely on the expertise of our colleagues in pathology to correctly identify the cell of origin. Histologic diagnosis of malignancy starts with identification of general morphology with hematoxylin and eosin (H+E) staining. In one series, light microscopy alone categorized 60% of tumors as adenocarcinoma, 5% as squamous cell carcinoma, and the remaining 35% as the less definitive categories of poorly differentiated adenocarcinoma, poorly differentiated carcinoma, or poorly differentiated neoplasm [1].

Immunohistochemical testing using antibodies to probe cell surfaces refines the diagnosis and most often determines the origin of the malignancy. For example, staining for the cell surface protein S100 identifies malignant melanoma [2]. Cytokeratin staining identifies broad categories of adenocarcinoma, and there are over 20 commonly assayed cytokeratin markers. Figure 1.1 identifies a diagnostic algorithm based on staining for CK-7 and CK-20, two commonly used cytokeratins, in carcinoma of unknown primary.

In many malignancies, molecular features of the tumor provide prognostic and predictive information that impacts treatment. For example, breast adenocarcinoma is characterized by the presence or absence of estrogen and progesterone receptors, which are predictive of response to adjuvant selective estrogen receptor modulators (SERMs) such as tamoxifen or aromatase inhibitors (AIs) such as anastrozole [3, 4]. Overexpression of the epidermal growth factor receptor (EGFR)-family

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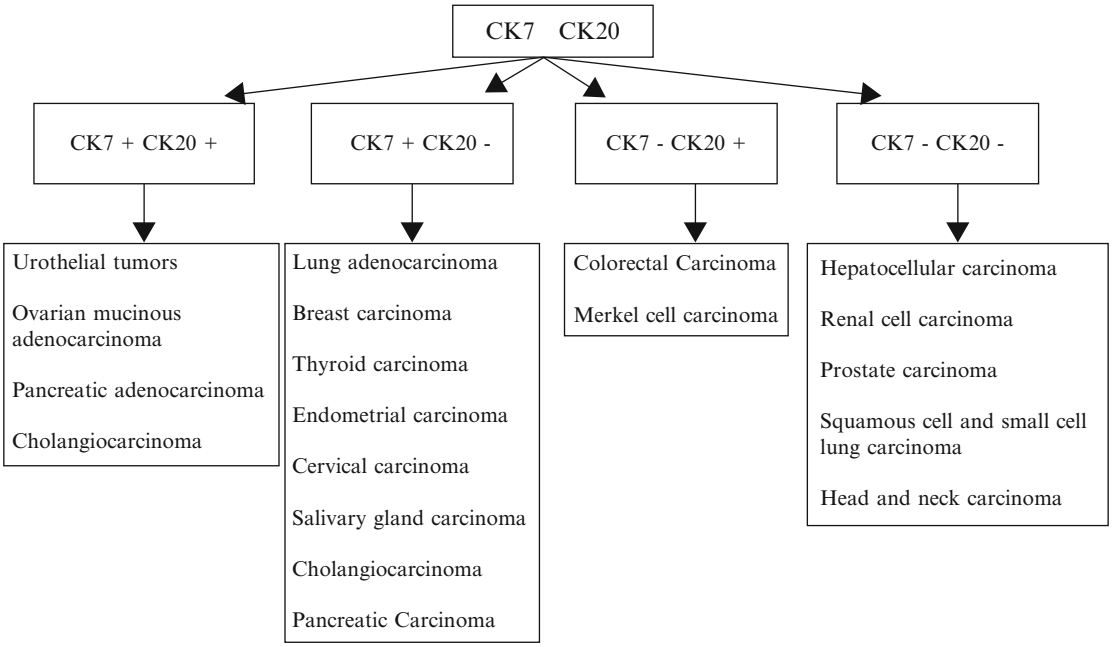

Fig. 1.1 Cytokeratin staining can help categorize malignancy (Reprinted with permission from Varadhachary GR, Abbruzzese JL, Lenzi R. Diagnostic strategies for unknown primary cancer. Cancer. 2004;100(9):1776–85.)

member protein HER2/neu predicts benefit of that anti-HER2 antibody trastuzumab (Herceptin) [5]. The benefit of trastuzumab in tumors overexpressing HER2 was recently demonstrated in locally advanced and metastatic gastric cancer as well [6]. HER2 status is assayed by two means – immunohistochemistry to assess for receptor density, and polymerase chain reaction (PCR) to assess for gene amplification, as shown in Fig. 1.2.

Oncogene mutations can predict response, or resistance, to therapy. In lung cancer, activating mutations in the EGFR predict for response to anti-EGFR tyrosine kinase inhibitors (TKIs) erlotinib (Tarceva, OSI Pharmaceuticals, Melville, New York) and gefitinib (Iressa, AstraZeneca, London, United Kingdom) in the first-line, most commonly in never-smokers [7, 8]. In contrast, activating mutations in the KRAS oncogene in colorectal cancer, present in approximately 40% of tumors, predict resistance to anti-EGFR therapy with the monoclonal antibody cetuximab [9]. Both EGFR and KRAS mutations are assessed using sequence-specific PCR-based techniques.

Once a histologic and molecular diagnosis is established, formal staging follows. Staging guidelines are disease-specific, but most solid tumors follow the American Joint Committee on Cancer (AJCC) TNM system. Notably, staging criteria differ depending on the type of cancer. T3N0M0 bladder cancer constitutes stage III disease, while T3N0M0 colon cancer is stage II, and T3N0M0 breast cancer (but also T3*N1*M0) is stage II. Exceptions to TNM staging should be noted – cancers of the brain and spinal cord are classified according to their cell type and grade; the Ann Arbor staging classification is commonly used to stage lymphomas; and staging is not relevant for most types of leukemia [10].

Patient Assessment

When a diagnosis is made and the stage is confirmed, treatment planning begins. Before selecting chemotherapy and establishing the multidisciplinary treatment approach, the oncologist must first consider the patient's larger context.

Defining Goals of Care

When malignancy is diagnosed at an earlier stage and cure is possible, most patients will opt for this approach. However, when cancer is detected at an advanced stage, the choice of therapy can be less straightforward. Consultation with the patient and his/her family is undertaken to outline options and to establish reasonable *goals of care*. Is the patient interested in

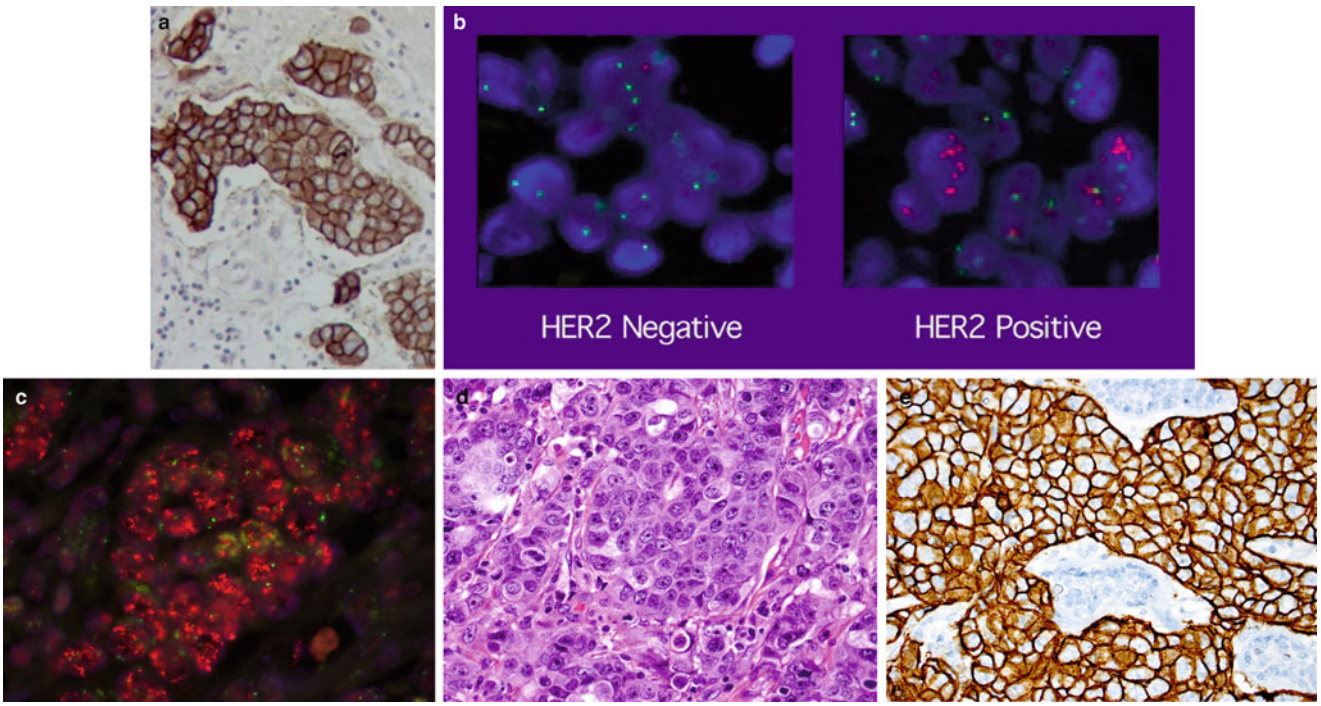

Fig. 1.2 (**a**) HE (hematoxylin and eosin) stain shows high-grade invasive ductal carcinoma of the breast with diffuse growth of pleomorphic tumor cells and frequent mitotic figures. (**b**) HER2 immunohistochemistry shows strong (3+) circular membranous staining of tumor cells. (**c**) HER2 fluorescence in-situ hybridization (FISH) shows amplification of HER2 signals (*orange*), compared with chromosome 17 signals (*green*) with amplification ratio of 9.7 [Vysis HER2 probe]. (**d**, **e**) HER2 immunohistochemistry and FISH (Images courtesy of Elena F. Brachtel, MD, Breast Pathology, Massachusetts General Hospital.)

pursuing an aggressive treatment strategy that is most likely to prolong survival, but in the interim involve potentially the greatest toxicity and the most intense need for medical follow-up? Does he/she favor a treatment that maximizes quality of life but perhaps offers less robust survival benefit? Or, does the patient wish to refrain from intensive medical intervention altogether, favoring a supportive care approach, which focuses exclusively on symptom reduction and optimizing time at home? Difficult, but important, discussions around goals are crucial at the outset of treatment, and discussions evolve with the patient's clinical course.

Identifying Medical Comorbidities

The oncologist must consider the patient's medical comorbidities in treatment planning, considering the specific toxicities of potential therapy in the context of the patient's overall health. Baseline renal or hepatic dysfunction – the latter often related to metastatic disease in the liver – often requires chemotherapy dose-reduction. Organ dysfunction may impact the choice of therapy. For example, patients with advanced colorectal cancer with liver involvement and hepatic dysfunction are often initiated on combination therapy with 5-FU/leucovorin and oxaliplatin (FOLFOX) rather than the equally efficacious 5-FU/leucovorin and irinotecan (FOLFIRI) regimen, because high bilirubin and alkaline phosphatase levels are associated with an exponential decrease in the clearance of irinotecan, and drug toxicity (neutropenia, diarrhea) correlates with serum bilirubin concentration [11]. Drugs such as doxorubicin and trastuzumab, both associated with onset of congestive heart failure, are contraindicated in patients with this preexisting condition [12, 13]. Bleomycin, which is associated with the rare but serious complication of pulmonary fibrosis, is contraindicated in patients with underlying pulmonary disease, and pulmonary function testing is compulsory prior to starting treatment [14, 15].

Medical comorbidities can impact the choice of treatment modality altogether. In patients with potentially resectable (Stage I–Stage IIIA) lung cancer, patients with significant smoking history and related comorbidities [chronic obstructive pulmonary disease (COPD) with diminished pulmonary reserve or severe cardiovascular disease] are at times deemed "medically inoperable" and their multidisciplinary treatment shifts from potentially curative surgery toward chemotherapy, radiation, and local ablation approaches, with inferior outcomes [16, 17].

Fig. 1.3 Eastern Cooperative Oncology Group performance status (ECOG PS) scale

0 - Asymptomatic (Fully active, able to carry on all pre-disease activities without restriction)
1 - Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work)
2 - Symptomatic, <50% in bed during the day (Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours)
3 - Symptomatic, >50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours)
4 - Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair)
5 - Death

Assessing Performance Status

Oncologists must continually evaluate the patient's fitness for treatment. Several validated instruments provide objective scoring of overall fitness, including the Karnofsky performance status (KPS) and the Lansky score in children. The Eastern Cooperative Oncology Group performance score (ECOG PS) is most commonly used by medical oncologists and has been demonstrated to most directly correlate with outcome [18]. ECOG PS is used to assess overall wellness, ability to conduct activities of daily living, strength, and mobility, as outlined in Fig. 1.3.

Patients with ECOG PS 0 or 1 are generally cleared for treatment without concern. Patients with ECOG PS 2 may struggle with treatment, and it becomes an individualized decision with the oncologist, patient, and family. Single-agent chemotherapy or single-agent biologic therapy with demonstrated activity (such as cetuximab therapy in head and neck cancers) may be given in the setting of a borderline patient who might be harmed by aggressive multiagent cytotoxic therapy [19]. Patients with an ECOG PS 3 or above are generally considered unfit for most therapies, and treatment may hasten morbidity and even mortality without offering potential benefit. During the course of treatment and especially in the setting of progressive metastatic disease, a patient's ECOG PS may decline, and chemotherapeutic options that were once appropriate are no longer safe. This is a very common juncture for discussion of transition to best supportive care and hospice care, in which the focus is shifted from life-prolonging treatment toward intensification of symptom control and comfort.

Patients with a small minority of disseminated but highly chemoresponsive tumors constitute an exception to the rule. For example, patients with extensive stage small cell lung cancer may be offered chemotherapy even when very ill, with potential reduction of tumor burden that results in a tremendous improvement in overall health. Hematologic malignancies (most notably lymphoma) and germ cell tumors follow this same logic.

Treatment Planning

The multidisciplinary treatment approach incorporates chemotherapy, surgery, radiation, and local treatments in a stepwise or concomitant fashion that is specific to the malignancy, stage, and patient.

Adjuvant therapy refers to treatment administered after resection of the primary tumor, but for whom odds of cure are increased with additional therapy. Selecting patients who would derive benefit from adjuvant chemotherapy means assessing recurrence risk – the goal being to screen out patients with such a low recurrence risk that the toxicity of therapy outweighs its benefit. Lymph node-negative, hormone-receptor positive breast cancer patients are assessed for adjuvant therapy based on primary tumor size and tumor grade. Equivocal cases may benefit from the use of the Recurrence Score assay (Oncotype Dx), in which the primary tumor is subjected to a 21-gene expression assay which assigns a recurrence score [20]. Figure 1.4 demonstrates a schematic of the genes that comprise the 21-gene recurrence score. A similar instrument was approved in Stage II colon cancer in 2010, and similar diagnostics are being explored in lung and other malignancies. For higher-risk patients, however, the benefit to adjuvant chemotherapy has been clearly demonstrated in multiple malignancies such as breast, lung, and colon.

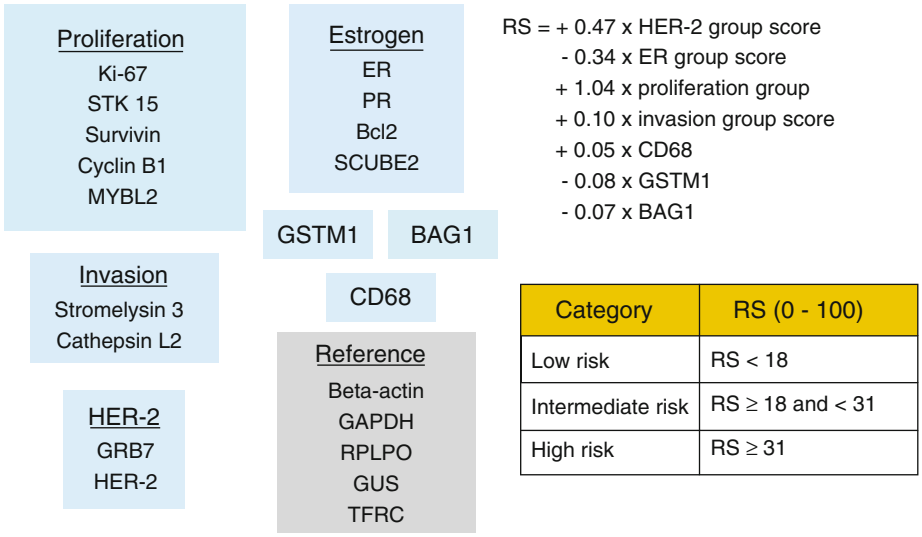

Fig. 1.4 Oncotype Dx recurrence score: schematic of a 21-gene assay

Neoadjuvant (preoperative) therapy is delivered prior to surgical resection of the primary tumor in order to reduce tumor bulk and allow for a more definitive resection. In rectal cancer, neoadjuvant chemoradiation has provided superior postoperative outcomes in terms of both local recurrence and likelihood of sphincter preservation for patients with T3/4 rectal tumors [21]. The accuracy of magnetic resonance imaging (MRI) or endoscopic ultrasound (EUS) staging for rectal cancer is critical to the multidisciplinary management of these patients [22]. For bulky stage III tumors of the breast, neoadjuvant chemotherapy improves likelihood of successful resection [23].

Palliative therapy is comprised of chemotherapy and radiation administered to the patient in whom surgical intervention with curative intent is not possible, either due to extent of metastatic disease or to medical nonoperability. Targeted treatments such as irradiating bony metastases reduce pain. Systemic chemotherapy can also reduce symptoms and prolong survival. Patients are informed that the goal of therapy is to help them live "as well as possible for as long as possible". Gemcitabine, the current mainstay of treatment for pancreatic adenocarcinoma, was demonstrated in a landmark trial that resulted in its approval to prolong life expectancy in a small subset, but more broadly offer "clinical benefit," defined as improvement in pain, performance status, or weight [24].

Introduction to Therapeutics

The treatment options in oncology have expanded tremendously over the past few decades. Cytotoxic chemotherapy remains the mainstay of treatment for some malignancies such as lung and colon cancer. In contrast, it plays little role in the treatment of renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC), where treatment targeting the biochemical pathway driving the cancer (targeted therapy) has become the primary treatment modality. Regardless of method, cancer therapies share the goal of inducing cancer cell death. The mechanisms of action of each therapy will be outlined in this section.

The *fractional cell kill hypothesis*, studied most extensively in leukemia and lymphoma, is an important guiding principle for therapy. The hypothesis holds that for any given concentration of chemotherapy, a set fraction of cells will be killed, independent of the total number of cells. The same set fraction of cells will be killed with the next cycle of therapy, and so on. Of course, malignant tumors exhibit continued cell division in the midst of therapy. The number of treatments, and the interval between treatments, are determined by the theoretical time required to reduce the cell population to zero – but accounting for the tolerance of the host for *toxicity* incurred by the therapy itself [25].

The "therapeutic index" of cytotoxic chemotherapy is defined as the differential between the toxic dose and the therapeutic dose. The fundamental problem in cancer treatment – and the root of most toxicity – is the inability to differentiate malignant cells from those of the normal healthy host, resulting in a narrow therapeutic index. As most chemotherapy targets cells with rapid turnover, toxicities stem from injury to normal tissues with high turnover that are caught in the crossfire – bone marrow, hair follicles, gastrointestinal (GI) mucosa, and the reproductive organs. Managing chemotherapy-associated toxicity means both controlling symptoms and minimizing treatment delays and dose reductions.

Table 1.1 Antimetabolites commonly used in solid tumors

Group	Agent	Common cancers	Common toxicities
Pyrimidine analogs	5-Fluorouracil	Breast GI Head and neck	Diarrhea Mucositis Myelosuppression
	Capecitabine	Breast GI	Diarrhea Mucositis Myelosuppression Hand-foot syndrome
	Gemcitabine	GI Breast Lung Ovary Bladder	Flu-like syndrome Myelosuppression
Purine analogs	6-MP fludarabine	Leukemia	
Antifolates	Methotrexate	Bladder Breast	Myelosuppression Mucositis
	Pemetrexed	NSCLC Bladder Mesothelioma	Myelosuppression Fatigue Rash

GI gastrointestinal; *NSCLC* non-small cell lung cancer

The stakes of treatment interruption in the setting of toxicity are dependent on the goals of therapy. Adjuvant treatment such as dose-dense adriamycin/cyclophosphamide in breast cancer or definitive treatment with curative intent – for example, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R-CHOP) in lymphoma or bleomycin/etoposide/cisplatin (BEP) in testicular cancer – have the best odds of cure when delivered *on schedule* at *full dose*. For this reason, patients are given growth factor support with granulocyte-colony stimulating factor (G-CSF) for low white blood cell counts and transfused red blood cells for severe anemia. In contrast, chemotherapy that is delivered in the noncurative setting (i.e., palliative chemotherapy) is at times held or dose-reduced for toxicity. When a curative endpoint is elusive, optimizing symptom control is the top priority.

The fractional cell kill hypothesis does not hold entirely true in solid malignancy, as tumors are heterogenous, necrotic, and avascular – the very properties that require multidisciplinary approaches including interventional oncology to deliver toxic doses of therapy for local eradication. What follows is a short primer on the major classes of cytotoxic chemotherapy, primarily restricted to drugs used in the treatment of solid tumors – i.e., cancers in which interventional oncologists play a direct role in treatment. Please consult more definitive texts for detailed review of chemotherapy activity and toxicity [25, 26].

Antimetabolites (including antifolates) mimic naturally occurring components of cellular replication and metabolism. Analogs of purines and pyrimidines, the building blocks of DNA and RNA, are incorporated into growing strands, terminating replication, and ultimately resulting in cell death – though the main activity of the pyrimidine analog 5-FU is likely the inhibition of thymidylate synthetase (TS) enzyme itself. Antifolates, such as methotrexate and pemetrexed, interfere with reduction of folate to the biologically active tetrahydrofolate, an essential cofactor for DNA synthesis (Table 1.1).

The major classes of *antimicrotubule agents* are the taxanes and the vinca alkaloids. Microtubules are comprised of tubulin dimers and provide the lattice for DNA replication during mitosis, and have an equally important role in the structure of the nondividing cell. Taxanes exert their effect on the microtubule by paradoxically stabilizing the microtubule spindle apparatus and preventing depolymerization, disrupting the orderly disassembly of the spindle apparatus necessary for completing mitosis [27]. In contrast, vinca alkaloids prevent microtubule assembly by binding beta tubulin and preventing subunit dimerization and microtubule polymerization – impeding mitosis and ultimately resulting in apoptosis (Table 1.2).

Topoisomerase inhibitors exert their effects during DNA synthesis. DNA topoisomerase I is a nuclear enzyme that relieves torsional strain in DNA during replication and transcription by complexing with a single strand of DNA to allow its complementary strand to uncoil around, or pass through, the complex. Camptothecins bind to and stabilize the topoisomerase–DNA complex, preventing dissociation and resulting in double-strand breaks. Similarly, anthracyclines, once thought to intercalate DNA due to their planar structure, likely exert their main effect by binding topoisomerase II and creating strand breaks by binding and stabilizing the Topo-II–DNA complex. Etoposide binds the Topo-II complex and inhibits 5′ to 3′ reannealing after the necessary strand breaks for uncoiling are made, propagating strand breaks and leading to apoptosis (Table 1.3).

Alkylating agents and platinum analogs exert their effect by covalently altering and crosslinking the strands of DNA. As a class, they are notable for their indiscriminate tissue toxicity and steep dose–response curve – high-dose alkylators are used as conditioning (myeloablative) agents in preparation for stem cell rescue in hematologic malignancy. Classic alkylators such

Table 1.2 Antimicrotubule agents commonly used in solid tumors

Group	Agent	Common cancers	Common toxicities
Taxanes	Paclitaxel	Lung Breast Ovarian Bladder Endometrial GI	Hypersensitivity Myelosuppression/neutropenia Bradyarrhythmias Neuropathy
	Docetaxel	Breast Lung GI Head and neck	Edema/third spacing Ascites, pleural effusion Myelosuppression/neutropenia Neuropathy
Vinca alkaloids	Vinblastine	Bladder (MVAC)	Myelosuppression
	Vinorelbine	Breast Lung	Myelosuppression

GI gastrointestinal; *MVAC* methotrexate, vinblastine, adriamycin, and cisplatin

Table 1.3 Topoisomerase inhibitors commonly used in solid tumors

Group	Agent	Common cancers	Common toxicities
Anthracyclines	Doxorubicin	Breast Bladder Endometrial Sarcoma	Myelosuppression Alopecia Mucositis Cardiomyopathy
	Epirubicin	Esophageal/gastric Breast	MDS/AML
Camptothecins	Irinotecan	GI SCLC	Diarrhea Myelosuppression
	Topotecan	SCLC NSCLC Platinum-resistant ovarian Endometrial	Myelosuppression – high prevalence of Grade 4 neutropenia
Derivatives	Etoposide (VP-16)	NSCLC SCLC Ovarian Testicular	Myelosuppression LFT abnormalities MDS/AML

GI gastrointestinal; *SCLC* small cell lung cancer; *NSCLC* non-small cell lung cancer; *MDS/AML* myelodysplastic syndrome/acute myeloid leukemia; *LFT* liver function test

as the nitrogen mustards (cyclophosphamide and chlorambucil) become unstable when enzymatically activated, adding a chloroethyl group to electronegative segments of DNA. The chloroethyl moieties subsequently crosslink strands of DNA, making excision repair difficult to execute, ultimately leading to apoptosis. Nonclassical alkylators, such as dacarbazine and its derivative temozolomide, are prodrugs that when enzymatically activated, methylate the DNA base pairs guanine and adenine, leading to aberrant DNA crosslinking. Platinum compounds exert this same net effect by depositing platinum complexes within DNA (Table 1.4).

Targeted Therapy

Our expanding knowledge of cancer biology has initiated development of therapies that target biologic pathways, and their use has transformed medical oncology. Molecular targeted therapies include monoclonal antibodies (MAb) such as the anti-EGFR antibodies cetuximab and panitumumab and the antivascular endothelial growth factor (anti-VEGF) antibody bevacizumab; small molecule inhibitors of tyrosine kinases (TKIs) such as the BCR-Abl/c-kit TKI imatinib, anti-EGFR TKIs gefitinib and erlotinib, and the multitarget TKIs sunitinib and sorafenib; and the proteasome inhibitor bortezomib.

Renal cell carcinoma and hepatocellular carcinoma, two cancers in which interventional oncologists play a central role in treating, have demonstrated greatest benefit from targeted therapy where cytotoxic therapy has provided minimal or no benefit.

Table 1.4 Alkylating agents and platinum analogs commonly used in solid tumors

Group	Agent	Common cancers	Common toxicities
Nitrogen mustards	Cyclophosphamide	Breast	Myelosuppression Hemorrhagic cystitis Alopecia
	Ifosamide	Sarcoma Testicular	Myelosuppression Hematuria
Nonclassical alkylators	Dacarbazine (DTIC)	Melanoma Sarcoma	Myelosuppression LFT abnormalities
	Temozolomide	Glioblastoma Melanoma	Nausea/vomiting Headache Myelosuppression
Platinum analogs	Cisplatin	Lung Bladder Head and neck Esophagus Cervix Biliary tract Endometrial Mesothelioma Testicular	Nausea/vomiting Ototoxicity Nephrotoxicity
	Carboplatin	Lung Ovary Endometrial Head and neck Testicular	Myelosuppression Nausea/vomiting
	Oxaliplatin	GI Head and neck	Transient cold-induced peripheral neuropathy Irreversible neuropathy Myelosuppression

GI gastrointestinal; *LFT* liver function tests

In patients with advanced, unresectable hepatocellular carcinoma in whom liver-directed therapy is also inappropriate, single-agent chemotherapy including doxorubicin, 5-FU, and cisplatin, and combination regimens with gemcitabine/oxaliplatin and cisplatin, alpha-interferon, doxorubicin, and 5-FU (PIAF) all failed to demonstrate meaningful response rates and overall outcomes [28–30]. Sorafenib, a multitargeted TKI with activity against vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor (PDGF), Raf, and c-kit was Food and Drug Administration (FDA) approved after the European Sorafenib Hepatocellular Carcinoma Assessment Randomized Protocol (SHARP) trial, a study of 602 patients with inoperable HCC, demonstrated an overall survival benefit in the sorafenib-treated patients (10.7 months versus 7.9 months with best supportive care alone) [31]. Notably, radiographic response was very low in this study (and in a Phase II study that preceded it), and survival correlated more directly with serum alpha-fetoprotein levels than with Response Evaluation Criteria in Solid Tumors (RECIST) response.

Renal cell carcinoma, with the exception of sarcomatoid and collecting duct subtypes, is generally deemed chemo-resistant, and immunotherapy with IL-2 and interferon-alpha comprised the mainstay of therapy until 2006. Advances in understanding the central role of the angiogenesis pathway highlighted the potential for targeting the VEGF and mammalian target of rapamycin (mTOR) pathways in this disease, and has led to the approval of sunitinib, sorafenib, temsirolimus, and bevacizumab in the first- and second line for treatment of advanced RCC [31–35].

Measuring the Impact of Therapy

Assessing whether treatment has had its intended effect is dependent on the stage of cancer being treated. The success of the *adjuvant* treatment of resected cancers is measured by disease nonrecurrence over a lifetime. In some cancers (e.g., triple-negative breast cancer), survival beyond 5 years portends outright cure. Paradoxically, estrogen receptor/progesterone receptor (ER/PR) positive cancers, while more indolent upfront, tend to have a longer risk-period for recurrence out to 15–20 years after adjuvant treatment [36]. Malignancies such as high-risk melanoma have a lifelong risk of recurrence.

4.3.1. Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the *smallest sum on study* (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (*Note:* the appearance of one or more new lesions is also considered progression).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Fig. 1.5 European Organisation for Research and Treatment of Cancer (EORTC) response evaluation criteria in solid tumors (RECIST) criteria for target lesion evaluation (October 2008)

After neoadjuvant or adjuvant treatment, monitoring serum tumor markers can provide an ongoing assessment of disease burden. For example, prostate-specific antigen (PSA) should become undetectable after radical prostatectomy, and a rise in PSA over time suggests local recurrence or metastatic disease [37]. Serum carcinoembryonic antigen (CEA) is followed in Stage II/III colorectal cancer after surgery and chemotherapy, with guidelines mandating monitoring at 3-month intervals for the first 2 years after completion of therapy, and then at 6-month intervals up to 5 years [38]. In ovarian cancer, patients with Stage III disease who have been treated with cytoreductive surgery followed by adjuvant platinum-based chemotherapy are monitored traditionally for cancer antigen 125 (CA-125) level, but recent data suggest that following patients clinically (close follow-up for symptoms) rather than with tumor markers does not impact their survival when a recurrence is detected [39]. Some, but not all, malignancies benefit from serial imaging to monitor for potential disease recurrence.

In patients with metastatic cancer, success of palliative therapy is measured by several metrics; first, clinical: assessing for symptom improvement and pain control; second, radiologic: evidence of chemotherapy response (tumor shrinkage) or disease stabilization. In the setting of a clinical trial, the European Organisation for Research and Treatment of Cancer (EORTC) RECIST criteria are used to assess response to therapy – criteria well-known to radiologists and reviewed in Fig. 1.5. The criteria mandate a two-dimensional change in the sum of target lesions greater than 30% to constitute partial response and radiologic disappearance to constitute a complete response to treatment [40]. Outside of clinical trials, medical oncologists still rely on correlative imaging to document stable disease, tumor shrinkage, or progression, but precise volumetric criteria are not as relevant.

With the advent of biologic therapy, the RECIST criteria for tumor volume assessment may be less sensitive, because the biologic mechanism of therapy may not directly induce tumor shrinkage. As mentioned above, RECIST was inadequate as a sole metric for sorafenib response in HCC in the SHARP trial. In another retrospective study of 234 patients with advanced colorectal cancer with liver metastasis treated with chemotherapy plus bevacizumab, RECIST criteria were predictive of complete or major pathologic response (documented on subsequent resection of metastases) but less sensitive for detecting minor pathologic response – as most patients fell into the "stable disease" RECIST category. In contrast, newer morphologic criteria, in which optimal response to therapy is defined as a change in metastases from heterogenous and thick, with irregular borders into bland, homogenous lesions with sharp interface with surrounding liver parenchyma, had greater sensitivity to detect minor pathologic response [41]. Positron emission tomography (PET), dynamic contrast enhanced MRI, and molecular imaging techniques will undoubtedly continue to advance our understanding of "response" in the era of targeted therapy.

As our understanding of the molecular biology of cancer therapy progresses, we are entering an era of personalized cancer medicine. Tumor genetics are used increasingly to determine both prognosis and choice of treatment. Metrics such as standard RECIST criteria, while sufficient to assess response to cytotoxic therapy, are being reevaluated in the context of targeted agents. Most importantly, patients are living longer with malignancy, and local treatment of metastatic disease is becoming more prevalent. Medical oncologists and interventional oncologists will continue to foster collaboration and improve patient outcomes in the years to come.

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