

# Cellular Mechanisms of Chemotherapy

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## Introduction

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Cancers are a growth of abnormal cells, arising mostly from genetic alterations that lead to unregulated cell growth, invasion, and metastasis. According to the American Cancer Society's (2014) *Cancer Facts and Figures*, more than 1.6 million new diagnoses of invasive cancer and more than 580,000 deaths were estimated to occur in 2014. The encouraging news is the continued decline in cancer deaths for all sites among men and women and nearly all racial and ethnic groups (Jemal, Ward, & Thun, 2010). This improvement is a result of tobacco prevention and control efforts, screening and early detection, and significant improvements in treatment for many types of cancers (Eheman et al., 2012). A consortium of six U.S. research groups conducted a study that showed approximately 795,851 deaths were averted by tobacco control efforts (Moolgavkar et al., n.d.). Although many people will never receive a cancer diagnosis, many others will require treatment for this stealthy and clandestine disease. These treatments may include surgery, radiation, chemotherapy, and immunotherapy.

Chemotherapy continues to play a key role in the treatment plan for most patients with cancer. The goals of chemotherapy include cure, control, and palliation. Effective cancer chemotherapy works by inhibiting cancer cell proliferation and growth with limited toxicity to the host patient (Moolgavkar et al., 2012; Skeel, 2011). An understanding of the biology of cancer, the mechanisms of action, and the purpose of chemotherapy helps the nurse in developing a personalized plan of care for each patient. This chap-

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ter provides an overview of cancer in terms of normal and malignant cell growth, the role of the immune system, the effect of chemotherapy on malignant cells, and treatment response criteria, as well as the therapeutic goals of treatment.

## Normal and Malignant Cell Growth

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Carcinogenesis is a multistep process arising from cells that involves the disruption of apoptosis (programmed cell death), self-sufficiency in growth signaling, insensitivity to antigrowth signals, tissue invasion, metastasis, and a limitless potential for replication and sustained angiogenesis (Hanahan & Weinberg, 2000). Cells in the human body may replicate 40–60 times before they reach the Hayflick limit (when cell division stops) and enter the senescence phase, leading to cell death. The parent stem cells provide a pool of dividing cells to replace those that have died (Hayflick, 1965; Hayflick & Stanbridge, 1967). Normal cell division is a process that must be completed with consistent conformity through distinct phases. These steps include gap 0 ( $G_0$  resting phase, also known as quiescence), gap 1 ( $G_1$ ), synthesis (S phase), gap 2 ( $G_2$ ), and mitosis (M) (Weinberg, 1995). The progression through this process is strictly controlled by several checkpoints and regulated by cyclin-dependent kinases (CDKs), which are activated by proteins known as cyclins (Schwartz, 2008) (see Figure 1-1).

## The Cell Cycle

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Prior to initiation of the cell cycle, there is an interphase where cells take in nutrients in preparation for cell division. The first phase,  $G_1$ , takes place from the end of mitosis to the beginning of DNA synthesis. This phase is marked by the synthesis of 20 amino acids that form millions of proteins and enzymes required for S phase DNA replication. Tumor suppressors and transcription factors that direct the genes to replicate, or in some cases repress replication, tightly regulate the process from  $G_1$  to synthesis. Also in this phase, the  $G_1$  checkpoint acts as a control mechanism to ensure readiness for DNA synthesis. The S phase starts with the identical replication of chromosomes to create two daughter chromatids. A chromatid is one-half of two normally identical copies of a replicated chromosome (King, 2006; Wagner, Berliner, & Benz, 2008). In S phase, DNA is doubled and the cell is very sensitive to external stress, including chemotherapy.  $G_2$  is the biosynthesis of microtubules, the structural components of the cell that have specific polarity required for mitosis. RNA and protein synthesis occur in preparation for mitosis. The  $G_2$  checkpoint control mechanism ensures readiness before entering mitosis, and inhibition of the  $G_2$  phase

**Figure 1-1. The Cell Cycle**

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prevents mitosis. The  $G_2$  checkpoint control mechanism is also known as the  $G_2$  restriction point. When DNA becomes damaged, it triggers a cellular response known as the post-replication checkpoint where post-replication repair can occur before the damage is passed to daughter cells (Callegeri & Kelly, 2006). If metabolic or oncogenic stress is detected, it induces *TP53* function, which can express genes to induce apoptosis, cell growth arrest, and angiogenesis (Song, Samulski, & Van Dyke, 2008). Mitosis is a fundamental process of life. Mitosis includes prophase, metaphase, anaphase, and telophase (see Figures 1-1 and 1-2).

- Prophase: Material to make chromosomes, known as chromatin, begins to condense in the nucleus. Tiny cylinders that create spindle fibers, known as centrioles, move to opposite ends of the cell and fibers extending become the mitotic spindle.
- Metaphase: Spindle fibers align the chromosomes along the middle of the cell nucleus to create a metaphase plate.

**Figure 1-2. Major Events in Mitosis**

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- Anaphase: The paired chromosomes move to the opposite sides of the cell.
- Telophase: The daughter chromatids with one-half of the chromosome DNA arrive at the opposite poles of the cell and new membranes form around the daughter nuclei (Karp, 2013; Reed, 2011).

The process of mitosis duplicates all nuclei contents, including chromosomes, and splits daughter nuclei into two identical daughter cells. This nuclear division, also known as karyokinesis, allows for the separation of chromosomes in the cell nucleus into two identical nuclei. Following mitosis, the division of the nuclei, cytoplasm, organelle, and cell membrane into two cells is known as cytokinesis. Cytokinesis results in genetically identical daughter cells with 23 pairs of chromosomes (Cooper & Hausman, 2006; Song et al., 2008).

Regulation of the cell cycle occurs through CDKs, which are present throughout cellular division. Proto-oncogenes and tumor suppressor genes (TSGs) are two major gene types that exert their effects on growth through the control of cell division and apoptosis. Proto-oncogenes code for proteins that will signal cell growth and differentiation. When mutated, they become oncogenes that cause a loss of cell regulation and allow abnormal gene duplication (Longo, 2012). The normal function of TSGs is to restrain cell growth. Based on the initial theory of the Knudson two-hit hypothesis, both copies of chromosomes of the TSG need to be inactivated for cancer to occur (Knudson, 1971). More recent research by Berger, Knudson, and Pandolfi (2011) shows that even partial inactivation of tumor suppressors can significantly contribute to malignant cell development.

Cancer arises when a single clonal cell obtains advantage over normal cells through 5–10 accumulated genetic mutations that allow progression to a fully malignant phenotype (Morin, Trent, Collins, & Vogelstein, 2012).

These mutagenic cells evade the immune system and are able to alter the microenvironment to create growth factors and blood supply that promotes malignant growth.

## **Immunology: Host Defense**

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The immune system is a remarkable defense mechanism that responds rapidly to potential pathogens. The immune system is divided into an innate immune system and an acquired or adaptive immune system that consists of both humoral and cellular components (Janeway, Travers, Walport, & Shlomchik, 2005). The mechanisms of immunity respond to a vast array of clinical conditions including recovery from infectious diseases, allergies, transplantation of tissue, and rejection of malignant cells (Place, Huh, & Polyak, 2011). For this to occur, it is essential that the immune system determines self from nonself. The sophisticated system also has immunologic memory after an initial response to a pathogen by adapting or acquiring an enhanced response to subsequent exposures (see Table 1-1).

### ***Innate Immunity***

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The first defense to outside insult, the skin, provides a physical barrier and produces microbial factors. This innate response is activated by pattern recognition receptors (Kurt-Jones et al., 2000). Pathogens that enter the epithelium are met with microbial sensors and large white blood cells. The response is immediate, nonspecific, and does not have long-lasting memory. Once in the body, pathogens are met with inflammation that increases blood flow, bringing in the complement system cascade to attack the membrane surface with antibodies in a rapid killing response. Leukocytes (white blood cells), macrophages, and dendritic cells combine in phagocytosis to engulf and digest the pathogens. Macrophages also act as both scavengers and antigen-presenting cells that activate the adaptive immune system (Alberts et al., 2002). The adaptive or acquired immune system is a second tier of defense.

### ***Adaptive and Acquired Immunity***

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The immune system consists of lymphocytes with specific roles in defense. These cells reside in the spleen, lymph nodes, intestines, and tonsils. Lymphocytes circulate in the blood and lymph to deliver immunocompetent cells directly to the site where needed. Activated lymphocytes can enter tissue, where they eradicate local infections. Memory lymphocytes patrol and

<b>Table 1-1. Immune System Cells and Their Function</b>
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scan tissue for specific antigens. The two classes of lymphocytes include B lymphocytes and T lymphocytes. B lymphocytes, which mature in the bone marrow, are involved in the humoral immune response to make antibodies that bind to antigens by membrane-bound receptors known as immunoglobulins (Radoja, Frey, & Vukmanovic, 2006). The B lymphocytes do not need antigen processing because they have an antibody on their surface. Immunoglobulins activate the complement system, which is responsible for allergic inflammation and as membrane receptors for antigens (Radoja et al., 2006). Coordination of these responses and communication takes place through a soluble network of mediators known as cytokines. Cytokines are secreted by immune cells and promote the proliferation of T cells.

T lymphocytes, via the thymus, are involved in cell-mediated immune response by expressing important helper function and aid in production of antibodies by B cells. T lymphocytes learn recognition of self from nonself in the thymus (Workman, Szymczak-Workman, Pillai, & Vignalim, 2009). The two major subtypes are killer T cells and helper T cells. These cells recognize molecules and mediate the function of antigen-presenting cells. Killer T cells are activated when they bind to specific antigens, then travel through the body in search of cells that bear the same antigen (Andersen, Schrama, Straten, & Becker, 2006). They then release cytotoxins into the surface, essentially imploding them, causing death. Helper T cells regulate both the innate and adaptive immune response. They have no cytotoxic ability but direct other immune responses to perform this function for them (Radoja et al., 2006). They play an important role in tumor cell cytotoxicity. Transformed cells of tumors have antigens that are not recognized as self. Examples of these foreign antigens are viruses such as human papillomavirus, tyrosinase expressed from mutant skin cells in melanoma, and growth signal proteins expressed as oncogenes (Andersen et al., 2006; Renkvist, Castelli, Robbins, & Parmiani, 2001). These antigens are shed and detected in the body by patrolling immune cells. This process is initiated by the macrophage presenting a malignant cell to the T lymphocyte. After the T lymphocyte is exposed to the malignant cell antigen, it produces T lymphocytes and B cells that are specific to the antigen. The B cells connect to the cancerous cell in a lock-and-key function, flagging the cell for destruction (Renkvist et al., 2001). Activated T cells bind to the antigen receptor on the malignant cell surface to allow destruction by killer T cells.

## Cellular Transformation to Malignancy

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When the immune system fails to remove malignant cells, they are allowed to proliferate. The transformation of a cell from normal to malignant has distinct phenotypic characteristics that arise predominantly from genetic mutations. These genetic abnormalities allow for uncontrolled cell repli-

cation, tissue invasion, and metastasis. Malignancy originates from genetic instability of a single cell or clonal origin that becomes abnormal (Cooper & Hausman, 2013; King, 2006). Epigenetic changes are critical for cancers to arise. Deregulation of cell proliferation may be caused by a loss of response to growth regulators or an increased response to growth proliferators. This leads to loss of normal checkpoint responses (Cooper & Hausman, 2013).

Arrest of the cell before complete differentiation allows the cell to maintain stem cell properties permitting it to use chromosomal instability and translocations in developing malignant cell programming (Geigl, Obenaus, Schwarzbraun, & Speicher, 2008). This can lead to loss of apoptotic pathways that gives malignant cells a survival advantage and allows for clonal expansion within the tumor. Malignant cells may no longer respond, have normal apoptosis, or cell death pathways. Research shows that cells have a process known as autophagy, second death, which rids the body of undesired cells (Danial & Korsmeyer, 2004). In cancer, autophagy may allow the malignant cells to digest organelles as a survival mechanism in response to nutrient starvation (Danial & Korsmeyer, 2004). It is easy to imagine this being a factor in rapidly growing tumors that become necrotic at the center when they grow too fast for nutrients to reach all cells. Genetic instability is another characteristic that allows for DNA mutations and chromosomal instability (Geigl et al., 2008). Several examples of this are *TP53* or *BRCA1/2* mutations, mismatch repair genes, and loss of spindle checkpoints. Loss of replicative senescence means malignant cells may not stop dividing or have a resting,  $G_0$ , phase. An example of this is the TP53 protein that regulates *BRCA1* transcription allowing for *BRCA1*-associated breast cancer. Approximately 5%–10% of breast cancers are hereditary and associated with this mutation (Lakhani et al., 2002; National Cancer Institute [NCI], 2009).

## Cancer Physiology

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Normal cells are limited in their rate of growth because of cell-to-cell transduction signaling that keeps them oriented to the appropriate size, function, and location (Place et al., 2011). The lack of oxygen and nutrients limits excessive growth. Malignant cells acquire functional capabilities that allow self-sufficiency in growth signals and become insensitive to antigrowth signaling (Kees & Egeblad, 2011). They also evade apoptosis, have limitless potential for replication, have sustained angiogenesis, and invade tissue to metastasize (Place et al., 2011). Tumor cells' expression of pro-angiogenic genes causes increased angiogenesis, which can occur at many stages of the tumor progression pathway. Tumors that acquire angiogenic ability or an angiogenic switch gain access to the host blood supply by invading the endothelial basement membrane and allowing capillary sprout (Bergers & Benjamin, 2003; Holmgren, O'Reilly, & Folkman, 1995).

Cell-to-cell signaling occurs through a gap junction or nexus that allows electrical and metabolic communication between cells (Laird, Castillo, & Kasprzak, 1995). The connection and communication between cardiac cells and neuronal synapses is one example of this process working effectively. Intravasation through the walls of nearby lymph and blood vessels is an example of the system failing. Dysplastic cells become malignant through loss of gap junction adhesion allowing extravasation and motility of cancer cells (Christofori & Semb, 1999). *Invasion* refers to direct migration and penetration by cancer cells into the local extracellular matrix and surrounding tissue (Chambers, Groom, & MacDonald, 2002). The malignant tumor cell is then only limited by its ability to survive in a foreign environment. *Metastasis* refers to the ability of cancer cells to penetrate into lymphatic and blood vessels, circulate through the bloodstream, and colonize distant metastatic sites (Song et al., 2008).

Cells send signals from extracellular and intracellular receptors and direct cell-to-cell communication through signal transduction. Signal transduction is a cascade of chemical messaging that allows regulation of cell differentiation, division, and cell death, or apoptosis (Karp, 2013). Transduction begins with a signaling molecule making contact with the cell's surface receptor on the extracellular matrix in a process called *receptor activation*. These signals can originate remotely or from the cell itself through autocrine signaling (Ertel, Verghes, Byers, Ochs, & Tozeren, 2006).

Growth factor signaling is mediated by cell surface growth factor receptors possessing tyrosine kinase activity. The cell's plasma transmembrane spans the surface of the cell. Ligands (stimulating proteins) binding outside the cell stimulate a series of events inside the cell's cytoplasm. Receptor tyrosine kinases (RTKs) are transmembrane proteins that have both an extracellular receptor that is capable of binding to ligands outside the cell surface and an internal kinase domain that signals into the cell nucleus. RTKs are responsible for most major signal transduction pathways (Drasin, Robin, & Ford, 2011). To perform signal transduction, phosphorylation of tyrosine allows a downstream cascade into the cytoplasm to facilitate cell differentiation and metabolism. *Phosphorylation* is the addition of a phosphate group to a molecule or protein, which provides energy to turn protein enzymes on and off (Haura et al., 2010). Two examples of key signal transduction pathways are Janus kinases 1 and 2 (JAK1/2) and transforming growth factor-beta (TGF- $\beta$ ).

JAK2 is a tyrosine kinase receptor that is essential for cytokine signaling and phosphorylation and directly regulates gene transcription (Wallace & Sayeski, 2006). JAK-deficient progenitors fail to respond to erythropoietin, thrombopoietin, and granulocyte macrophage-colony-stimulating factor, leading to an absence of hematopoiesis. *Hematopoiesis* is the production, multiplication, and specialization of blood cell development in the bone marrow. Alterations in this function are found in polycythemia vera, es-

sential thrombocytopenia, myelofibrosis, and myeloproliferative disorders (Kralovics et al., 2005). The discovery of JAK1/2 mutations and the development of targeted therapies could improve treatment of myeloproliferative and myelofibrotic disorders of the marrow.

TGF- $\beta$  is involved in adult and embryo development through cell growth, cell differentiation, and apoptosis (Biswas et al., 2004). Downstream transduction signals cell cycle checkpoints that arrest cell growth. Without this process functioning correctly, the tumor suppressor function allows carcinogenic replication (Berger et al., 2011). The result of this error allows TGF- $\beta$  to switch from a tumor suppressor to a tumor promoter. Mutations in type II TGF- $\beta$  are present in 80% of patients with colorectal cancer (Biswas et al., 2004; Saif & Chu, 2010). For additional information on signaling pathways, see Table 1-2.

## Histology of Cancer

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Defining the origin of cancer involves establishing the *histology*, the study of tissues and cells under a microscope, in order to determine the precise classification of a tumor. At the inception of an embryo, three germ layers give rise to cells, tissues, and organs. The first layer, ectoderm, differentiates into the skin and nervous system. The second layer, the mesoderm, differentiates into connective tissue and bone, blood and lymph, and cartilage, fat, and muscle. The third layer, the endoderm, becomes the digestive and respiratory tracts (Andreeff, Goodrich, & Koeffler, 2010). Tumors from a specific histologic tissue often have microscopic features similar to that tissue. For example, a carcinoma would arise from the epithelium, whereas a sarcoma is derived from connective tissue. The nomenclature used refers to differentiation of the tissue from which the tumor derived. The prefix gives further delineation to the type of tissue the tumor arose from. For example, *adeno-* means glandular epithelium, *osteo-* means bone, and *lipo-* means fat. Suffixes may provide additional information; *-oma* means tumor, and *-sarcoma* means connective tissue malignancy. When the histologic examination shows very poor differentiation, it is known as anaplastic because it does not resemble any normal tissue (Andreeff et al., 2010; Krafts, 2009).

The Human Genome Project, an international collaboration, has identified every chemical base, approximately 25,000 genes, in the human genome. This research has driven efforts to create the Cancer Gene Census, which is an ongoing effort to catalog genes that cause mutations and have a clinical association with cancer. These maps are redesigning the tumor taxonomy by moving it from a histologic base to a genetic-based level. This information is creating an environment of personalized cancer medicine by using tumor genotyping to help decide the best treatment for each patient (Samuels, Bardelli, & López-Otín, 2011).

The next wave of personalized treatment will be based on epigenetics. The study of epigenetics is focused on understanding inheritable changes

<b>Table 1-2. Examples of Cancer Signaling Pathways</b>
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in cells caused by mechanisms other than permanent changes in the DNA. Epigenetics is proving that cancerous changes can be passed from cell to cell without altering the permanent genetic makeup, and these changes contribute to progression of disease and resistance to therapy (Kumari et al., 2013; Minucci & Pelicci, 2006).

## Goals of Chemotherapy

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The goals of chemotherapy include prevention, cure, control, and palliation. Cancer prevention is action taken to reduce the chance of getting cancer. This includes changes in diet and lifestyle, early identification of precancerous conditions, and chemoprevention. An excellent example of this is the 6.7% age-adjusted reduction in breast cancer in 2003 following the national decline in the use of hormone replacement therapy (Ravdin et al., 2007). Chemoprevention refers to medicines that treat a precancerous condition to delay or prevent cancer occurrence. Tamoxifen, the first chemoprevention drug approved by the U.S. Food and Drug Administration, reduces the occurrence of breast cancer in high-risk women by half (Ravdin et al., 2007). A person is considered high risk when he or she has a family history of cancer, an inherited genetic mutation, or a previous diagnosis of precancerous cellular changes. Age, ethnicity, obesity, and smoking are also factors that increase the risk for developing cancer (NCI, 2006).

The goals of treatment (cure, control, and palliation) are based on the biologic behavior and extent of the malignancy, the efficacy of available therapies, the mortality or morbidity associated with the therapy, and the patient's performance status and preferences (Simon, Watson, Drake, Fenton, & McLoughlin, 2008). Providing treatment with a curative intent implies there is a reasonable expectation based on clinical studies that treatment will likely eliminate the cancer and it will not return. Both adjuvant and neoadjuvant chemotherapy is given with the goal of cure and control of risk for recurrence. Adjuvant chemotherapy is given after the surgical removal of a cancer to eradicate any residual cancer cells that may be left. Neoadjuvant chemotherapy is given before surgery to reduce the size of the tumor so that it is easier to remove with surgery. Chemotherapy is given to control cancer with the expectation that the cancer may not completely go away but will be controlled to allow the patient to have improved quality of life and potentially a longer survival living with cancer as a chronic disease. The word *palliate* comes from the Latin word *palliare*, meaning "to cloak" ("Palliate," n.d.). When chemotherapy is given as palliation, the goal is to relieve symptoms and improve quality of life. The World Health Organization (2012) defines palliative care as

An approach that improves the quality of life of patients and their families facing the problem associated with life-threatening

illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual. (para. 1)

These treatment goals may be achieved with the use of chemotherapy alone or with the addition of molecularly targeted agents, surgery, or radiation.

## Evaluation of Response to Treatment

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It is essential that patients understand and agree with their treatment plan and goals. If the disease is limited, a patient may benefit from local, adjuvant systemic therapy or neoadjuvant therapy. A simple example of this is a woman with a small breast cancer. Radiation to the breast is an example of local therapy when the goal is to eradicate or locally control the disease. After the initial intervention, some patients can achieve cure through adjuvant systemic therapy intended to destroy any remaining subclinical cells that may have spread to other areas. Adjuvant treatment is given in addition to the main treatment. If surgery is the main treatment to remove any evidence of a tumor, then radiation or chemotherapy would be the definitive adjunct therapy to ensure occult cells are eradicated. Neoadjuvant therapy is an option for some women who want breast-conserving surgery. When chemotherapy is given first, before surgery, it may shrink or pathologically remove any sign of the cancer. After neoadjuvant chemotherapy, having no pathologic evidence of malignancy is considered a pathologic complete response (pCR). Having a pCR may result in both superior disease-free survival and improved aesthetic outcome following reconstructive surgery (von Minckwitz et al., 2012).

Systemic therapy given to treat cancer can be evaluated in several ways. Two common methods are clinical benefit response and Response Evaluation Criteria in Solid Tumors (RECIST). In some cases, patients may see benefit from reduced pain, improvement in their activity tolerance, and overall well-being even if no measurable change is seen radiographically in the disease. This is known as clinical benefit response. Although very subjective, even when treatment may not have a significant impact on disease, patients may experience an improvement in symptoms, performance status, and quality of life (Eisenhauer et al., 2009).

RECIST, presented by the American Cancer Society in 1999, are the result of a task force with the European Organization for Research and Treatment of Cancer and the National Cancer Institute of Canada Clinical Trials Group. The main objective was to create a set of criteria that could be used to evaluate treatment response in solid tumors (Eisenhauer et al., 2009). Evaluating tumor response may affect treatment in three ways. First, it is

used to evaluate objective tumor response as a prospective endpoint in clinical trials when determining if a new therapy has the efficacy to continue in study. Second, it is used to evaluate specific subsets of patients that are randomized and compared to current treatments. In this setting, time to progression, disease response rates, disease-free survival, and overall survival can be studied. Third, and possibly the most critical for individual patients, it guides clinicians and patients in decisions about continuation of current therapy (Therasse et al., 2000). In simple terms, RECIST defines complete remission (CR) as confirmed disappearance of disease, partial remission (PR) as a 30% decrease in disease, stable disease (SD) as neither PR nor progressive disease (PD), and PD as 20% increase with no CR, PR, or SD documented before increased disease (Eisenhauer et al., 2009). In some instances, other grading criteria may be used in clinical trials based on the type and extent of disease studied, the ability to reliably measure the disease, location of target lesions, and internal review board or clinical investigator preference (Perceptive Informatics, n.d.).

Another tool for determining the presence of disease and response to therapy is the tumor marker. Tumor markers are substances found in the body when cancer is present. For tumor markers to be valuable, they must have high sensitivity and specificity. They may be used for screening, to subjectively determine if a patient is deriving benefit from a treatment, and to detect early evidence of recurrence. Examples of tumor markers are prostate-specific antigen, cancer carbohydrate antigen 125 used as a biomarker for ovarian cancer, alpha-fetoprotein in diagnosing hepatocellular cancer, and carcinoembryonic antigen for colon cancer (Harris et al., 2007). Not every patient has elevated tumor markers at diagnosis or when the tumor burden increases; therefore, clinicians also must rely on physical examination, radiologic evidence, and pathologic evaluation of suspicious findings.

### **Cell Cycle Specificity**

Chemotherapeutic drugs can be placed into two main categories that relate to cell cycle: cycle nonspecific and cycle specific (see Table 1-3). Cycle-nonspecific drugs have a linear response curve meaning that the more drug that is given, the greater the cell kill (Howland & Mycek, 2006). Cycle-nonspecific drugs, such as alkylating agents, antitumor antibiotics, hormonal therapies, and nitrosoureas, exert their effect in all phases of the cell cycle, including the  $G_0$  resting phase. They are effective for both high and low growth fraction malignancies. Cell cycle-specific drugs, such as antimetabolites and plant alkaloids, exert their effect within a specific phase of the cell cycle. They can cause cell injury only if present during a specific phase in the cell cycle. A typical malignant cell spends approx-

imately 40% of the time in  $G_1$  for synthesis of cellular components needed for DNA synthesis (may vary greatly depending on tumor type), 39% of the time in synthesis replicating the DNA genome, 19% of the time in  $G_2$  synthesizing cellular components for mitosis, and only 2% of the time in mitosis leading to differentiation or cycle rest (Chu & Sartorelli, 2012). Because of this restriction, these drugs may have limited ability despite in-

**Table 1-3. Examples of Cell Cycle–Specific and Cell Cycle–Nonspecific Anticancer Drugs**

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**Table 1-3. Examples of Cell Cycle–Specific and Cell Cycle–Nonspecific Anticancer Drugs (Continued)**

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creased dose. An example is fluorouracil, which is cell cycle S-phase specific. However, if the drug is administered over a period of time and the concentration is maintained, the cell kill may be greater (Howland & Mycek,

2006). Table 1-3 lists common cell cycle–specific and cell cycle–nonspecific chemotherapeutic agents used in cancer treatments, which are covered in more detail in later chapters.

### ***Factors Affecting Chemotherapy Response***

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The goal of cancer therapy is to prevent the disease from overtaking the host. “The goal in selecting an effective drug, therefore, is to find an agent that has marked growth-inhibitory or controlling effect on the cancer cell and minimal toxic effect on the host” (Skeel, 2011, p. 1). Halting the process of multiplication, invasion, and metastasis can occur in several ways, including inhibition of macromolecular synthesis and function, cytoplasmic organization, and cell membrane function (Workman et al., 2009). Interference with macromolecular synthesis and function refers to interference of the synthesis of DNA or RNA in the nucleus to trigger cell death. In a cell, the cytoplasm surrounds the nucleus and consists of a fluid called cytosol; organelles are suspended in it. The majority of cellular metabolism takes place within the cytosol, which includes the production of energy and the biosynthesis of nutrients (Workman et al., 2009). The cell membrane is a flexible layer that selectively controls the passage of chemicals and cell surface receptors into and out of the cell, thus maintaining homeostasis. Tumor burden, growth fraction, the use of single-agent or combination therapy, dose, and development of resistance of the disease to the drugs will affect cells’ responsiveness to chemotherapy (Chabner et al., 2006).

Optimal cancer therapy would eradicate all cancer cells without harming the normal cells of the host. Chemotherapy regimens provide patients with single agents or combinations of drugs, differing frequencies and dosage intensities, and therapeutic agents used to rescue the patient from toxicity. Combination chemotherapies are widely used in both solid and hematologic malignancies to optimize tumor cell kill. Reasons for using combination therapy include the prevention of resistant clones, increased cytotoxicity to resting and dividing cells, and enhancement of drug activity (synergism). Combination regimens allow chemotherapy to access tumor cell sanctuaries in the body by changing drug solubility or tissue affinity (Chu & Sartorelli, 2012).

Dosage and timing of drug delivery can be modified to affect chemotherapy response rates. Delivery of cell cycle–specific chemotherapeutic agents in intermittent doses to cells that have a shorter duration in the cell cycle may yield a lower number of cells killed. But if a cell cycle–specific agent is given via continuous infusion, it may result in a greater number of cells killed. A clear connection exists between the amount of chemotherapeutic agent and the cell death rate—the higher the dose, the

greater the number of cells killed (Howland & Mycek, 2006). Dose is determined in phase I clinical trials with the goal of high tumor cell death and limited host toxicity. Toxicity is the dose-limiting factor because it may lead to increased morbidity and mortality. *Dose intensity* is the total prescribed amount of chemotherapy delivered in a specific amount of time. Inadequate dosing can compromise the therapeutic benefit of the chemotherapy. *Dose-dense therapy* refers to a condensed schedule of treatment. For example, instead of patients receiving a prescribed regimen every three weeks, they would receive it every two weeks. Dose reductions and decreased dose rates are associated with compromised patient outcomes, whereas patients maintained in compliant regimens respond better (Howland & Mycek, 2006).

The tumor burden, or number of tumor cells present in a tumor, affects response to chemotherapy. Tumors have a growth rate, known as *growth fraction*, which results from the number of cells actively dividing in a specific period of time. Growth fraction and tumor size are inversely proportional to the chemotherapeutic response (Chu & Sartorelli, 2012). When the tumor is small, the growth fraction is fast. This allows for increased cell kill because an increased number of cells take up the drug. Under Gompertzian kinetics, the growth fraction of the tumor is not constant and peaks when the tumor is about one-third of its maximum size (Molski & Konarski, 2008). As the tumor grows, the growth fraction slows, and the response to chemotherapy is lessened. Greater tumor burden and slower growth fraction yield a greater potential for chemotherapy resistance (Chu & Sartorelli, 2012).

Chemotherapy resistance is a significant barrier to response. Malignant melanomas and renal cell cancers typically show a lack of response to conventional chemotherapy agents even with initial treatment. This is known as primary or inherent resistance. Acquired resistance occurs when a cancer cell is able to amplify a specific gene or when a receptor allows cells to evade the cytotoxic effects of therapy. Tumor heterogeneity, or genetic differences among individual cells, occurs because of mutations during the cell life cycle. These differences result in different growth rates, invasiveness and metastatic potential, hormone responsiveness, and susceptibility to chemotherapeutic agents. The mutations may result in resistance to chemotherapeutic agents (Chu & Sartorelli, 2012).

Overcoming drug resistance with the use of multidrug regimens optimizes cancer cell kill in different phases of the cell cycle. Another method of overcoming drug resistance is the use of chemosensitizers. Calcium channel blockers, such as verapamil, B vitamins (e.g., leucovorin), and warfarin, have been used to sensitize or modulate chemotherapy responses. A nonpharmacologic method of chemosensitization is radiation therapy because the cancer cells become very sensitive to destruction with radiation (Chu & Sartorelli, 2012; Howland & Mycek, 2006).

## Summary

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In his book *The Emperor of All Maladies: A Biography of Cancer*, Siddhartha Mukherjee (2010) described cancer as an incredible disease that is stitched into our genome. “Oncogenes arise from mutations in essential genes that regulate the growth of cells. Mutations accumulate in these genes when DNA is damaged by carcinogens, but also by seemingly random errors in copying genes when they divide” (Mukherjee, 2010, p. 462). The ability to understand cancer on a genomic level and effectively individualize treatment to a specific patient’s disease is a reality for some cancers, while researchers diligently continue their efforts to reach this breakthrough in treatment for others. Treatment planning for patients with cancer should involve interdisciplinary decision making with the patient at the core of the effort. This process should be based on an understanding of the immune system, which safeguards the body, and the origination, growth patterns, and communication cascades of malignant cells, along with cure and response rates (Bradley et al., 2002). Understanding treatment modalities and the many pathways by which cancers develop and proliferate improves nurses’ ability to communicate effectively with patients and the medical team. The ability to articulate intuitive nuances of critical thinking into descriptive interpretation of information is essential to patient outcomes. In the past decade, many new agents transformed the efficacy and tolerability of treatment. Research will continue to focus on the development of tools to identify those at risk, prevention of genetic abnormalities, and the development of molecular testing to identify those who will respond to treatment. The future holds the legacy of a multimechanistic approach to these problems.

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