Chemotherapy Agents: A Primer for the Interventional Radiologist

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ABSTRACT

In this article, the authors review the basic principles of cancer chemotherapy and provide an overview of each of the general classes of chemotherapeutic agents with a target audience of interventional radiologists in mind. Special attention is paid to agents used in regional chemotherapy as well as agents commonly included in systemic chemotherapeutic regimens for patients who also require regional chemotherapy.

KEYWORDS: Regional chemotherapy, principles of chemotherapy, cancer chemotherapy, chemotherapy review, chemotherapy agents

Objectives: Upon completion of this article, the reader should be able to define the general principles of chemotherapy and the classes of chemotherapeutic agents.

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In this article, we review the basic principles of chemotherapy and provide an overview of each of the general classes (Table 1) of chemotherapeutic agents. The administration of regional chemotherapy has become a major component of the clinical practice of interventional radiology (IR). As such, it has become important that interventional radiologists understand the general theory behind designing chemotherapeutic regimens, as well as the associated toxicity profiles. In the discussion of each of the general classes of chemotherapeutic agents, special attention has been paid to the specific agents that are in common use in the interventional suite.

GENERAL PRINCIPLES

Cell Biology and Division

Most chemotherapeutic agents affect either deoxyribonucleic acid (DNA) replication or protein synthesis in actively replicating cells. A brief review of cell biology will add meaning to the specific mechanisms of action discussed later.

The bulk of the life of a cell is spent in a resting, nonreplicating state called G₀ (G₀). Cells must replicate to replenish damaged/dying cells in the aging organism, which is accomplished through cell division. The term *cell cycle* refers to the active state of the cell

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Table 1 Classes of Commonly Used Chemotherapeutic Agents

Agent Class	Agent Used in IR	Clinical Application in IR	Adverse Effects
Alkylating agents		None common	Myelosuppression, GI symptoms, potential for sterility and carcinogenesis
Antimetabolites	5-fluorouracil	HIAC – HCC	Mucositis, GI symptoms, photophobia, cardiotoxicity, myelosuppression, dermatitis and alopecia
Natural products			
Plant alkaloids		None common	Peripheral neuropathy, mucositis, GI symptoms, diplopia, alopecia, headache
Antineoplastic antibiotics			
	Doxorubicin	TACE, DEB – HCC, cholangiocarcinoma, carcinoid, liver metastases (neuroendocrine tumors, sarcoma)	Cardiotoxicity, myelosuppression, alopecia, GI symptoms, red-tinged urine (not hematuria), palmar-plantar erythrodysesthesia
	Mitomycin C	HIAC, TACE – HCC, liver metastases (colorectal, ocular melanoma, neuroendocrine tumors)	Fever, anorexia, myelosuppression, hemolytic uremic syndrome, local hepatic arterial thrombosis
	Bleomycin	Pleurodesis of malignant pleural effusion	Fever, local pain
Other plant derivatives			
	Irinotecan	TACE – liver metastases from colorectal	Diarrhea, fever, myelosuppression, pancreatitis, thromboembolism, typhilitic colitis and toxic megacolon
Multikinase inhibitors			
	Sorafenib	None common in regional chemotherapy, but it is used in systemic regimens for HCC, RCC, and others	Diarrhea, weight loss, hand-foot skin reaction, hypophosphatemia, GI symptoms, myelosuppression, bleeding events
Platinum salts			
	Cisplatin	TACE – HCC, cholangiocarcinoma, carcinoid, liver metastases (neuroendocrine tumors, sarcoma)	Neurotoxicity, nephrotoxicity, myelosuppression, encephalopathy, seizures, GI symptoms
Hormones, hormone antagonists, and biologic agents			
	Bevacizumab	TACE – liver metastases from colorectal	hypertension, proteinuria, thrombosis, bleeding, wound healing complications, GI perforation, RPLS

DEB, drug-eluting beads; GI, gastrointestinal; HIAC, hepatic intraarterial chemotherapy; HCC, hepatocellular carcinoma; IR, Interventional Radiology; RCC, renal cell carcinoma; RPLS, reversible posterior leukoencephalopathy; TACE, transcatheter arterial chemoembolization.

(as opposed to the quiescent state) that results in cell division. Errors that occur during the cell cycle can result in unregulated cell growth and replication, and are a major contributor to the development of malignancy.

The cell cycle (Fig. 1) consists of four phases, which occur in a linear progression. These are GAP1 (G_1), synthetic phase, GAP2 (G_2), and mitosis. The “GAP” phases are so named because there is no microscopically obvious cell activity, and the phases were first described¹ before the regulatory molecular processes that occur during the periods named gaps were understood.²

It is now understood that during the G_1 phase, the cell rapidly replicates macromolecules to essentially double its internal components in preparation for cell division.³ During the synthetic phase, DNA is replicated/synthesized to double the complement of chromosomes. The G_2 phase includes complex regulatory steps such as a “checkpoint” that involves evaluation of replicated DNA for errors. During mitosis, the replicated chromosomes are pulled to opposite poles of the nucleus; following mitosis, the cell divides into two cells in a process called *cytokinesis*, and cell division is complete.

Figure 1 Cell cycle. The cell cycle is the sequence that results in the cell division. The straight lines each represent a single full complement of the cell's DNA, which is replicated in preparation for cell division during the synthetic phase.

Tumor Growth and Chemotherapeutic Strategy

The fraction of cells in a tumor that are actively replicating is referred to as the *growth fraction*. Because chemotherapy primarily affects cells that are actively replicating, growth fraction dictates what proportion of the tumor is susceptible to a given dose of chemotherapy. The growth fraction of a tumor has been demonstrated to decrease as a tumor grows larger, a concept that is called the Gompertzian model of tumor growth.⁴

The empiric theory used to explain the observed Gompertzian model of tumor growth is that tumor growth slows as the tumor outgrows its blood supply. Thus, a well-vascularized, small tumor has a higher proportion of cells actively replicating than it will when it grows larger. This makes smaller tumors more responsive to chemotherapeutic agents, and is the basis for the current preferred strategy of early, intensive chemotherapy when it is a viable option (as opposed to delayed or prolonged low-dose chemotherapy).

To achieve cure, chemotherapy regimens are designed aggressively with multiple, high-dose cycles. According to the Gompertzian model of tumor growth, as each cycle of chemotherapy is administered and tumor size decreases, each successive cycle should kill a larger proportion of the tumor cells than the previous. Complete tumor kill is the goal because, given Gompertzian dynamics, a near-complete response with a small number of residual tumor cells could result in the same volume of tumor in 5 years as a patient who had only a partial response and a large number of residual tumor cells. The smaller tumor grows faster than the larger tumor, and over time, they equalize in number of cells.

Although many regimens utilize high-dose chemotherapy cycles, there is some evidence that suggests that low-dose, slow infusions (metronomic) may be as or more effective than more aggressive dosing.

Another tenet of modern chemotherapy is the use of combination regimens, which are important for two reasons: synergism and resistance. Because different agents can act complementarily on different phases of the cell cycle, when administered together they can kill more tumor cells than the sum of the tumor kill that each

agent would inflict if given separately. For example, if a drug that impairs DNA synthesis is administered at the same time as a drug that impairs the separation of paired chromosomes, then both the cells that enter the synthetic phase and the cells that enter the mitotic phase while the drug is in the bloodstream will be killed. The second main reason combination regimens are important is that, like bacteria, tumor cells mutate and can develop drug-resistance. This resistance can occur even prior to drug exposure.⁵ Drug resistance is in fact the most common reason for failure of a chemotherapeutic regimen.⁶ Because of chemotherapeutic synergism and the speed at which tumors become drug-resistant, treatment with proven multidrug regimens is, in general, more effective than single-drug regimens.

Drug Choice

With regard to regional chemotherapy used in the clinical practice of IR, the choices in chemotherapeutic agents are generally limited to those that have proven effective in the setting of systemic therapy. An exception would be the situation in which a systemic therapy is effective but unable to be used routinely because the toxicity profile at the required doses is unacceptable. In this case, regional administration of that agent might allow sufficient drug concentration in the local environment of the tumor to achieve tumor kill while keeping the systemic concentration low enough to avoid the unacceptable side effects.

Pharmacokinetics and Pharmacodynamics

The pharmacokinetics and pharmacodynamics of a drug are important to consider when deciding the dose and route of administration. Pharmacokinetics refers to the absorption, distribution, metabolism, and excretion/elimination properties of a drug. Pharmacodynamics refers to the mechanism of action of the drug and the relationship between drug concentration and effects. In simpler terms, pharmacokinetics is what the body does to the drug, and pharmacodynamics is what the drug

does to the body. Doses must be adjusted for patients with impaired hepatic or renal function, or who have large fluid collections such as malignant pleural effusions or ascites that effect drug distribution.⁷

Regional Chemotherapy Administration

The two basic options in regional chemotherapy are direct percutaneous delivery to the tumor bed, and indirect delivery via arterial supply. Direct delivery is an uncommon application that is currently mainly limited to sarcomas and head and neck cancers. Indirect delivery via the arterial supply is the mainstay of interventional regional chemotherapy. Intraarterial chemotherapy works best in organs with dual blood supply, and is ideally used for hypervascular tumors. For example, hepatocellular carcinomas (HCC) receive most of their blood supply from the hepatic arteries, whereas the surrounding normal liver parenchyma receives most of its blood supply from the portal vein. As a consequence, interventions performed via hepatic arteries target HCC while relatively sparing normal liver parenchyma.

CLASSES OF AGENTS

Alkylating Agents

Alkylating agents kill cells by covalently binding hydrocarbons, or alkyl groups, to a cell's DNA. This causes DNA cross-links and strand breaks that result in either apoptosis (programmed cell death) or cell necrosis. Rapidly dividing cells are most susceptible to DNA alkylation, but alkylation can also occur in quiescent cells. Because there is some kill achieved in quiescent cells, some of the effects of alkylating agents are non-phase specific.⁸

The historical significance of alkylating agents warrants a brief aside. The alkylating agent "mustard gas" was first effectively weaponized by the Germans in World War I, but it was not until an incident during World War II that the potential therapeutic benefits were realized. In December 1943, a United States supply ship laden with mustard bombs was itself bombed in an aerial attack and sunk in an Italian harbor. The survivors, who had swum in the mustard-laden waters, experienced a drop in their white blood cell counts that was later connected to a potential therapy for lymphoma. Thus was the birth of modern cancer chemotherapy.⁹

Alkylating agents continue to be an integral tool in the systemic treatment of hematologic malignancies, where they are often used in combination due to their lack of cross-resistance. A subgroup of alkylating agents, the nitrosoureas, demonstrates lipophilicity; lipophilicity allows nitrosoureas such as carmustine to cross the blood-brain barrier, and is used to therapeutic advantage in the treatment of brain tumors.⁸ The clinical use of

alkylating agents requires a careful balance of therapeutic benefit against the near ubiquitous side effects of myelosuppression and immunosuppression. Because the mechanism of action involves DNA damage, a rare and not well-characterized additional potential side effect of alkylating agents is carcinogenesis. Alkylating agents are not commonly used in IR procedures at the time of this review.

Antimetabolites

Antimetabolites are agents that are structurally related to and compete with physiologic molecules in the formation of cellular macromolecules. The resultant macromolecules that incorporate antimetabolites into their framework lack the functionality of the normal corresponding cellular component. Most antimetabolites used in cancer chemotherapy affect DNA or ribonucleic acid (RNA) synthesis, and this is usually by either replacing a nucleotide (e.g., 6-mercaptopurine) or depressing nucleotide synthesis (e.g., methotrexate and 5-fluorouracil). DNA or RNA that incorporates nonphysiologic, antimetabolite nucleotides results in the formation of truncated cellular proteins, and ultimately apoptotic cell death. Because DNA synthesis occurs during the synthetic phase of the cell cycle, antimetabolites that act by this mechanism are cell-phase specific.

Antimetabolites are considered the most versatile drug class in chemotherapy,¹⁰ and they are used to treat a disparate group of tumors that includes lymphocytic leukemia, breast cancer, gastrointestinal (GI) adenocarcinomas, squamous cell carcinoma, and HCC. The role of antimetabolites in the treatment of HCC is of particular interest to interventionalists, who commonly use 5-fluorouracil (5-FU) in hepatic intraarterial chemotherapy (HIAC). Approximately 95% of a dose of 5-FU is absorbed by an HCC on first pass through the liver, which allows a high intratumoral concentration while maintaining a low systemic toxicity.⁷

Because the mechanism of action affects both tumor cells and normal cells in the synthetic phase of replication, and therapeutic regimens often require a prolonged period of drug exposure, side effects observed in antimetabolite therapy include myelosuppression, GI mucositis, and in the case of methotrexate (MTX), hepatic cirrhosis. A technique used to decrease the severity of the side effects in antifolate agents such as MTX is "leucovorin rescue." MTX competitively inhibits the enzyme that utilizes folate in the pathway that results in DNA nucleotide synthesis. MTX polyglutamates accumulate in tumor cells more than they accumulate in rapidly dividing normal cells, and this allows a "rescue" of the normal cells with administration of leucovorin (a physiologically active folate analogue).¹¹ Cancer cells, which cannot actively transport leucovorin, are exposed to the complete effects of MTX.

Natural Products

Natural products are chemotherapeutic agents derived from plants, fungi, or bacteria; these agents are diverse in their mechanisms of action. The two major categories of natural products are plant alkaloids and antineoplastic antibiotics.

Plant alkaloids such as vincristine, vinblastine, and paclitaxel inhibit the movement of microtubules, which form the cytoskeletal framework of a cell that allows intracellular transport of cellular components. Functional microtubules are crucial during mitosis because the microtubular mitotic spindle pulls replicated chromosomes to either side of the dividing cell. If transport of the replicated chromosomes is interrupted, the dividing cell cannot divide and the tumor cells cannot proliferate. Plant alkaloids exert their greatest effect during the mitotic phase of cell replication; however, because microtubules form the framework that allows intracellular transport in both quiescent and actively replicating cells, plant alkaloids are relatively nonphase specific.

Plant alkaloids are used extensively in systemic chemotherapy for a variety of neoplasms (e.g., leukemias, lymphomas, myeloma, breast, ovarian, brain, a wide range of childhood malignancies), and often in combination with other drug classes.¹² Oral formulations are precluded by the severe vesicant (epithelial blistering) effect of plant alkaloids, and currently administration is limited to the intravenous route. The dose-limiting toxicity in vincristine is a peripheral neuropathy that is common to all antimicrotubule agents because functional microtubules are required for intracellular axonal transport. Because the effect is an axonal length-dependent phenomenon, the neuropathy usually begins as paresthesias in the feet before progressing elsewhere, and persists for a variable period after completion of therapy.¹³ Plant alkaloids are not commonly used in IR procedures at the time of this review.

Antineoplastic antibiotics such as doxorubicin and mitomycin C are extracted from various species of the *Streptomyces* genus, which is a type of actinobacteria commonly found in soil and decaying vegetation. Interestingly, many non-antitumoral antibiotics such as vancomycin and amphotericin B are also derived from species of *Streptomyces*. Doxorubicin and mitomycin C are both used in the IR suite in hepatic intraarterial chemotherapy regimens, and a third antineoplastic antibiotic, bleomycin, is commonly used in pleurodesis.

Doxorubicin inhibits the action of DNA topoisomerase, which is an enzyme that relieves the torque on the DNA double helix that accumulates as the DNA is repeatedly unwound and rewound during transcription and replication. Topoisomerase relieves this torque by clipping the DNA helix, allowing the strand to unwind, and then re-annealing the free ends. Doxorubicin inhibits the re-annealing reaction, and the accumulation of DNA strand breaks ultimately leads to apoptosis or cell

necrosis.¹⁴ Doxorubicin is used extensively in systemic chemotherapy for a variety of tumor types, and dose-limiting toxicities include cardiotoxicity and myelosuppression. Intraarterial administration allows for high concentration delivery to the local tumor environment with relatively less systemic concentration and toxicity, and is used regularly in the treatment of HCC.

Mitomycin C is an antineoplastic antibiotic that causes DNA cross-links in a reaction similar to that which is observed with mustard alkylating agents. The reaction is best catalyzed in an oxygen-poor environment.¹⁵ Systemically, mitomycin C is used in combination regimens to treat breast, esophageal, and gastrointestinal cancer. Toxicity is predominantly related to delayed bone marrow suppression, the onset of which can be months after therapy.⁷ Mitomycin C is also used in hepatic intraarterial chemotherapy and chemoembolization.

Bleomycin incorporates free iron in the nucleus of the cell, and uses it as a substrate for a reductive reaction that produces free oxygen radicals. These oxygen radicals react with DNA and RNA to cause strand breaks that lead ultimately to cell death. Bleomycin is used in many systemic combination regimens, and the dose-limiting toxicity is a pulmonary toxicity that can lead to pulmonary fibrosis. In the interventional suite, bleomycin is used as a sclerosant in chemical pleurodesis in the treatment of malignant pleural effusion. Of the intracavitary dose delivered, approximately half enters into the systemic circulation.¹⁶

Platinum Salts

Platinum compounds cause intrastrand and interstrand cross-linkages in DNA that ultimately result in cell apoptosis. Platinum compounds enter the cell predominantly by passive diffusion.¹⁷ Once the compound diffuses into the cell nucleus, it binds to a guanine or adenine base on a strand of DNA, forming a DNA monoadduct. The monoadduct then binds to another guanine or adenine base on either the same strand or on the opposing strand in the DNA helix to form a cross-link. The interstrand crosslinks lock the two strands of the DNA helix together, which inhibits the action of the enzymes that unzip the DNA helix for DNA replication and transcription. The intrastrand crosslinks, which occur more readily than the interstrand crosslinks, cause an unnatural bend in the DNA helix that is thought to be recognized by enzymes that detect DNA damage that then reflexively trigger an apoptotic cascade.¹⁸ Platinum compounds cause apoptosis most readily in cells that are actively replicating, and are thus relatively cell-phase specific.

The platinum compounds currently approved for use in the United States are cisplatin, carboplatin, and oxaliplatin. They are used in combination regimens in a

wide variety of tumors. The toxicity profile includes severe nausea and vomiting invariably requiring antiemetic therapy, irreversible and cumulative ototoxicity, neurotoxicity that can result in seizures and dysrhythmias, and nephrotoxicity. Cisplatin was initially abandoned due to common acute renal failure, but now the nephrotoxicity is mitigated by aggressive hydration, which itself can be problematic due to volume overload. Cisplatin is often used in the treatment of liver tumors during hepatic chemoembolization procedures.

Multikinase Inhibitors

Protein kinases are transmembrane proteins that have an intracellular and an extracellular component that are used in cell signaling pathways, which include the pathways involved in cellular proliferation and differentiation. A component of the multistep carcinogenic pathway observed in HCC and many other cancers involves a mutation that results in the constitutive activation of one of these kinases such that it is always "on."¹⁹ This results in abnormal cellular proliferation and differentiation.

Sorafenib is an oral multikinase inhibitor of the receptor for VEGF (vascular endothelial growth factor) that also targets other tumoral cellular components. It is used in the systemic treatment of highly vascular tumors such as HCC and renal cell carcinoma. By inhibiting VEGF, sorafenib decreases tumor angiogenesis, which causes nutrient deprivation in tumor cells and resultant cell necrosis. Before sorafenib, there was no systemic chemotherapy available that was shown to have improved outcomes in advanced HCC. A placebo-controlled, multicenter study published in 2008 by Llovet et al demonstrated a mean 3-month increased survival time and time to radiologic progression in the treatment of HCC,²⁰ and now it is not uncommon for a patient who presents to IR for treatment of advanced HCC to be receiving this systemic agent as part of their regimen. Common side effects include diarrhea, weight loss, hand-foot skin reaction, and hypophosphatemia.

Biologic Response Modifiers and Hormonal Agents

Biologic response modifiers and hormonal agents include a diverse array of agents used in cancer treatment, and although they are not commonly used in locoregional therapy, the major classes will be discussed briefly for the sake of completeness. *Interferons* are powerful immunomodulators that activate cellular pathways that upregulate the innate immune system (T cells, macrophages, etc.) and are used to treat both hematologic malignancies and solid tumors.²¹ *Interleukin-2* enhances the cytolytic activity of cytotoxic and natural killer T-cells, and is used to treat metastatic melanoma and

metastatic renal cell carcinoma.²² *Histone deacetylase inhibitors* are an exciting new class of agents that affect the DNA packaging proteins required for transcription, and thereby cause arrest of cell growth and apoptosis.²³ *Monoclonal antibodies* are engineered to bind to receptors that are selectively expressed on the cell surface of some tumor types. Once bound to the tumor cell surface, the antibodies block growth receptor signaling in most cases (e.g., cetuximab and trastuzumab), although some agents work through an immunologic mechanism (e.g., rituximab). The primary effect leads to the lysis of the marked tumor cells; however, the receptors are found on many normal cell types as well (leading to common reactions such as rashes). Monoclonal antibodies are commonly used in combination regimens used to treat non-Hodgkin lymphoma (rituximab) and metastatic breast cancer (trastuzumab).²⁴ *Hormonal agents* manipulate the endocrine pathways of certain susceptible tumor types, and include the aromatase inhibitors used in receptor-positive breast cancer as well as the antiandrogens used to treat metastatic prostate cancer.²⁵

CONCLUSION

The image-guided, regional chemotherapeutic techniques used by interventional radiologists offer high-concentration, directed delivery of agents to local tumor environments. As the model of IR practice continues to shift into the realm of direct patient management, it has become increasingly important for the interventionalist to be familiar not only with the agents used in regional chemotherapy, but also with the systemic chemotherapy regimens that their patients are receiving.

REFERENCES

- Howard A, Pelc SR. Nuclear incorporation of P32 as demonstrated by autoradiographs. *Exp Cell Res* 1951;2(2):178-187
- Reed S. Cell cycle. In: De Vita V, Hellman S, Rosenberg S, eds. *Cancer: Principles & Practice of Oncology*. Philadelphia: Lippincott Williams & Wilkins; 2005:83
- Lees J. Control of the cell cycle. In: Abeloff M, Armitage J, Niederhuber J, Kastan M, McKenna W, eds. *Abeloff's Clinical Oncology*. 4th ed. Philadelphia: Churchill Livingstone/Elsevier; 2008:50
- Norton L. A Gompertzian model of human breast cancer growth. *Cancer Res* 1988;48(24 Pt 1):7067-7071
- Goldie JH, Coldman AJ. A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. *Cancer Treat Rep* 1979;63(11-12):1727-1733
- Kinsella AR, Smith D. Tumor resistance to antimetabolites. *Gen Pharmacol* 1998;30(5):623-626
- Ray C, Koczwara B. Principles of chemotherapy. In: Ray CE, Hicks ME, Patel NH, eds. *Interventions in Oncology*. Fairfax VA: Society of Interventional Radiology; 2003:9-15
- Huitema AD, Smits KD, Mathôt RA, Schellens JH, Rodenhuis S, Beijnen JH. The clinical pharmacology of

- alkylating agents in high-dose chemotherapy. *Anticancer Drugs* 2000;11(7):515-533
9. Hirsch J. An anniversary for cancer chemotherapy. *JAMA* 2006;296(12):1518-1520
 10. Kummur S, Noronha V, Chu E. Antimetabolites. In: De Vita V, Hellman S, Rosenberg S, eds. *Cancer: Principles & Practice of Oncology*. Philadelphia: Lippincott Williams & Wilkins; 2005:358
 11. Lennard L. Therapeutic drug monitoring of antimetabolic cytotoxic drugs. *Br J Clin Pharmacol* 1999;47(2):131-143
 12. Rowinsky E, Tolcher A. Antimicrotubule agents. In: De Vita V, Hellman S, Rosenberg S, eds. *Cancer: Principles & Practice of Oncology*. Philadelphia: Lippincott Williams & Wilkins; 2005:390-411
 13. Verstappen CC, Koeppen S, Heimans JJ, et al. Dose-related vincristine-induced peripheral neuropathy with unexpected off-therapy worsening. *Neurology* 2005;64(6):1076-1077
 14. Takimoto C. Topoisomerase interactive agents. In: De Vita V, Hellman S, Rosenberg S, eds. *Cancer: Principles & Practice of Oncology*. Philadelphia: Lippincott Williams & Wilkins; 2005:375-389
 15. Colvin O, Friedman H. Alkylating agents. In: DeVita V, Hellman S, Rosenberg S, eds. *Cancer: Principles & Practice of Oncology*. Philadelphia: Lippincott Williams & Wilkins; 2005:332-344
 16. Copur M, Rose M, Chu E. Miscellaneous chemotherapeutic agents. In: De Vita V, Hellman S, Rosenberg S, eds. *Cancer: Principles & Practice of Oncology*. Philadelphia: Lippincott Williams & Wilkins; 2005:417
 17. Gately DP, Howell SB. Cellular accumulation of the anticancer agent cisplatin: a review. *Br J Cancer* 1993;67(6):1171-1176
 18. Johnson S, O'Dwyer P. Cisplatin and its analogues. In: De Vita V, Hellman S, Rosenberg S, eds. *Cancer: Principles & Practice of Oncology*. Philadelphia: Lippincott Williams & Wilkins; 2005:344-358
 19. Ito Y, Sasaki Y, Horimoto M, et al. Activation of mitogen-activated protein kinases/extracellular signal-regulated kinases in human hepatocellular carcinoma. *Hepatology* 1998;27(4):951-958
 20. Llovet JM, Ricci S, Mazzaferro V, et al; SHARP Investigators Study Group. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;359(4):378-390
 21. Sondak V, Redman B. Pharmacology of cancer biotherapeutics. In: De Vita V, Hellman S, Rosenberg S, eds. *Cancer: Principles & Practice of Oncology*. Philadelphia: Lippincott Williams & Wilkins; 2005:423-430
 22. Mier J, Atkins M. Interleukin-2. In: De Vita V, Hellman S, Rosenberg S, eds. *Cancer: Principles & Practice of Oncology*. Philadelphia: Lippincott Williams & Wilkins; 2005:431-438
 23. Marks P, Richon V, Miller T, Kelly W. Histone deacetylase inhibitors: new targeted anticancer drugs. In: De Vita V, Hellman S, Rosenberg S, eds. *Cancer: Principles & Practice of Oncology*. Philadelphia: Lippincott Williams & Wilkins; 2005:439-445
 24. Cheng J, Adams G, Robinson M, Weiner L. Monoclonal antibodies. In: De Vita V, Hellman S, Rosenberg S, eds. *Cancer: Principles & Practice of Oncology*. Philadelphia: Lippincott Williams & Wilkins; 2005:445-456
 25. Goetz M, Erlichman C, Loprinzi C. Pharmacology of endocrine manipulation. In: De Vita V, Hellman S, Rosenberg S, eds. *Cancer: Principles & Practice of Oncology*. Philadelphia: Lippincott Williams & Wilkins; 2005:457-469