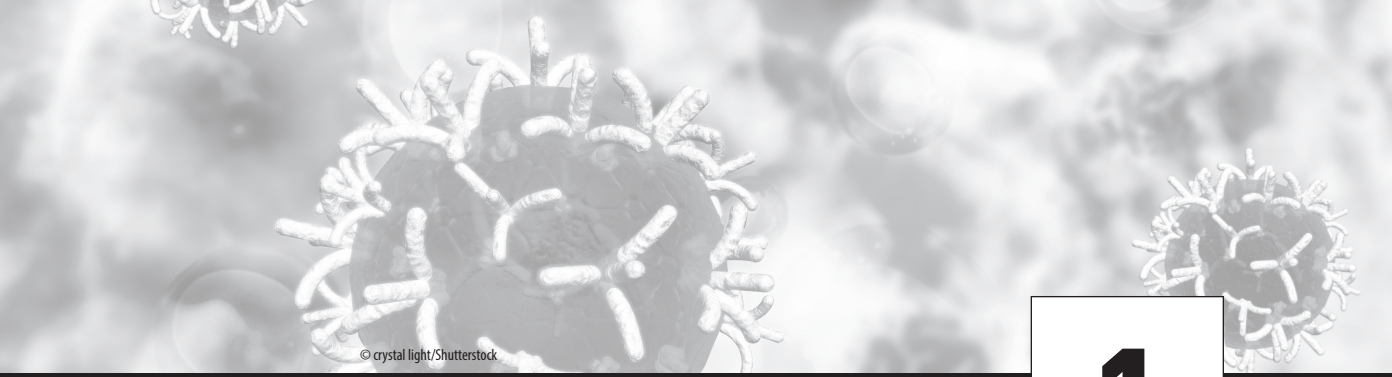

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Principles of Cancer Chemotherapy

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Introduction

The development of chemotherapy in the 1950s and 1960s resulted in curative therapeutic strategies for patients with hematologic malignancies and a small number of advanced solid tumors. These advances confirmed the principle that chemotherapy could indeed cure cancer and provided the rationale for integrating chemotherapy into combined-modality programs with surgery and radiation therapy in the early stages of disease to provide clinical benefit. Since its early days, the principal obstacles to the clinical efficacy of chemotherapy have been toxicity to the normal tissues of the body, tumor heterogeneity, and the development of cellular drug resistance. The development and application of sophisticated molecular technologies to analyze the gene expression of normal and malignant cells at the level of DNA, RNA, and/or protein have greatly facilitated the identification of some of the critical mechanisms through which chemotherapy exerts its antitumor effects and activates the program of cell death. The newer advances in molecular diagnostics, which now include next-generation sequencing, whole exome sequencing, and whole genome sequencing, have provided important new insights into the molecular and genetic events within cancer cells that can confer chemosensitivity to drug treatment as well as having identified potential new therapeutic targets. This enhanced understanding of the key molecular and signaling pathways by which chemotherapy, targeted therapies, biological therapies, and immunotherapy exert their antitumor activity, and by which genetic alterations can result in resistance to drug therapy, has provided the rational basis for developing innovative therapeutic strategies.

The Role of Chemotherapy in the Treatment of Cancer

Chemotherapy is presently used in four main clinical settings: (1) primary induction treatment for advanced disease or for cancers for which there are no other effective treatment approaches; (2) neoadjuvant treatment for patients who present with localized disease, for whom local forms of therapy, such as surgery and/or radiation, are inadequate by themselves; (3) adjuvant treatment to local treatment modalities, including surgery and/or radiation therapy; and (4) direct instillation into sanctuary sites or by site-directed perfusion of specific regions of the body directly affected by the cancer.

Primary induction chemotherapy refers to drug therapy administered as the primary treatment for patients who present with advanced cancer for which no alternative treatment exists. This has been the main approach to treat patients with advanced, metastatic disease. In most cases, the goals of therapy are to palliate tumor-related symptoms, improve overall quality of life, and prolong time to tumor progression (TTP) and overall survival (OS). Cancer chemotherapy is curative in a relatively small subset of patients who present with advanced disease. In adults, these potentially curable cancers include Hodgkin's and non-Hodgkin's lymphoma, germ cell cancer, acute leukemias, and choriocarcinoma, while the curable childhood cancers include acute lymphoblastic leukemia, Burkitt's lymphoma, Wilms' tumor, and embryonal rhabdomyosarcoma.

Neoadjuvant chemotherapy refers to the use of chemotherapy for patients who present with locally advanced cancer for which local therapies, such as surgery and radiation therapy, exist but are less than completely effective. The diseases for which a neoadjuvant approach is usually considered include anal cancer, bladder cancer, breast cancer, esophageal cancer, laryngeal cancer, locally advanced non–small cell lung cancer (NSCLC), and osteogenic sarcoma. For diseases such as anal cancer, gastroesophageal cancer, laryngeal cancer, and NSCLC, optimal clinical benefit is usually derived when chemotherapy is administered concurrently with radiation therapy.

One of the most important roles for systemic chemotherapy is in follow-up to local treatment modalities such as surgery and/or radiation therapy; this has been termed adjuvant chemotherapy. The development of disease recurrence, either locally or systemically, following surgery and/or radiation is mainly due to the spread of occult micrometastases. The goal of adjuvant therapy is to reduce the incidence of both local and systemic recurrence and to improve the OS of patients. In general, chemotherapy regimens with clinical activity against advanced disease may have curative potential following surgical resection of the primary tumor, provided the appropriate dose and schedule are administered. It is now well established that adjuvant chemotherapy is effective in prolonging both disease-free survival (DFS) and OS in patients with breast cancer, colorectal cancer (CRC), gastric cancer, NSCLC, Wilms' tumor, and osteogenic sarcoma. Adjuvant chemotherapy is also recommended in patients with anaplastic astrocytomas. Patients with primary malignant melanoma at high risk of developing metastases derive benefit in terms of improved DFS and OS from adjuvant treatment with the biologic agent α-interferon, although this treatment must be given for 1 year's duration. Recent studies have shown that the immune checkpoint inhibitors ipilimumab and nivolumab provide clinical benefit in the adjuvant treatment of surgically resected melanoma with lymph node involvement. The antihormonal agents tamoxifen, anastrozole, and letrozole are effective in the adjuvant therapy of postmenopausal

women whose breast tumors express the estrogen receptor. These agents must be administered on a long-term basis, with treatment being given for 5 years. Recent studies have shown that adjuvant therapy with imatinib for patients with surgically resected gastrointestinal stromal tumor (GIST) is more effective when given for 3 years as opposed to 1 year.

Principles of Combination Chemotherapy

With rare exceptions (e.g., choriocarcinoma and Burkitt's lymphoma), single drugs, at clinically tolerable doses, have been unable to cure cancer. In the 1960s and early 1970s, drug combination regimens were developed based on known biochemical actions of available anticancer drugs rather than on their clinical efficacy. Such regimens were, however, largely ineffective. The era of combination chemotherapy began when several active drugs from different classes became available for use in combination in the treatment of the acute leukemias and lymphomas. Following this initial success with hematologic malignancies, combination chemotherapy was subsequently extended to the treatment of solid tumors.

Combination chemotherapy with conventional cytotoxic agents accomplishes several key objectives not possible with single-agent therapy. First, it provides maximal cell kill within the range of toxicity tolerated by the host for each drug as long as dosing is not compromised. Second, it provides a broader range of interaction between drugs and tumor cells with different genetic abnormalities in a heterogeneous tumor population. Finally, it may prevent and/or slow the subsequent development of cellular drug resistance.

Certain principles have guided the selection of drugs in the most effective drug combinations, and they provide a paradigm for the development of new drug therapeutic regimens. First, only drugs known to be partially effective against the same tumor when used alone should be selected for use in combination. If available, drugs that produce some fraction of complete remission are preferred to those that produce only partial responses. Second, when several drugs of a class are available and are equally effective, a drug should be selected on the basis of toxicity that does not overlap with the toxicity of other drugs to be used in the combination. Although such selection leads to a wider range of side effects, it minimizes the risk of a potentially lethal effect caused by multiple insults to the same organ system by different drugs. Moreover, this approach allows dose intensity to be maximized. In addition, drugs should be used in their optimal dose and schedule, and drug combinations should be given at consistent intervals. The treatment-free interval between cycles should be the shortest possible time necessary for recovery of the most sensitive normal target tissue, which is usually the bone marrow. The biochemical, molecular, and pharmacologic mechanisms of interaction between the individual drugs in a given combination should be understood to allow for maximal effect. Finally, arbitrary reduction in the dose of an effective drug to allow for the addition of other, less effective drugs may dramatically reduce the clinical activity of the most effective agent below the threshold of effectiveness and reduce the capacity of the combination regimen to cure disease in a given patient.

One final issue relates to the optimal duration of drug administration. Several randomized trials in the adjuvant treatment of breast cancer and CRC have shown that

short-course treatment on the order of 6 months is as effective as long-course therapy (12 months). International Duration Evaluation of Adjuvant Therapy (IDEA) was a multi-national collaborative effort that showed that a shorter course of 3 months of adjuvant oxaliplatin-based chemotherapy yields the same level of clinical benefit as 6 months of treatment of stage III colon cancer. However, optimal duration may depend on the particular tumor type, as it is now well established that prolonged duration of adjuvant therapy in patients with surgically resected GIST, 3 years versus 1 year, results in improved clinical benefit. While progressive disease during chemotherapy is a clear indication to stop treatment in the advanced disease setting, the optimal duration of chemotherapy for patients without disease progression has not been well defined. With the development of novel and more potent drug regimens, the potential risk of cumulative adverse events, such as cardiotoxicity secondary to the anthracyclines and neurotoxicity secondary to the taxanes and the platinum analogs, must be factored in the decision-making process. There is, however, no evidence of clinical benefit in continuing therapy indefinitely until disease progression. A randomized study in metastatic CRC comparing continuous versus intermittent palliative chemotherapy showed that a policy of stopping and re-challenging with the same chemotherapy may provide a reasonable treatment option for certain patients. Similar observations have been observed in the treatment of metastatic disease of other tumor types, including NSCLC, breast cancer, germ cell cancer, ovarian cancer, and small cell lung cancer (SCLC).