Clinical Cancer Chemotherapy

Editor

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Note to the Reader

The science of medicine changes very quickly, and clinical research rapidly leads to expanded knowledge about drug therapy. Although the physicians who prepared this book and the publisher have made every effort to give you accurate information on dosages, precautions, and contraindications as of the time of publication, some dosages mentioned have been given in an investigational setting only; therefore, you are strongly urged to check the product information contained in the package of each drug prescribed. Only then can you be certain of obtaining the current official prescribing information for proper dosage recommendations, particularly for new or infrequently used drugs.

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Introduction

Few areas of clinical activity have been so persistently controversial and fraught with emotionalism as the field of cancer chemotherapy. Before World War II the cancer chemotherapist was generaliy deemed by his medical confreres to be a dreamer, a misguided fool, or a charlatan. The first effective control of an advanced human neoplasm was achieved in 1940 by Charles Huggins, who demonstrated the hormonal control of cancer of the prostate by orchiectomy and estrogen therapy. Stimulated by Huggins' monumental contribution, Nathanson, another surgeon, soon thereafter introduced hormonal manipulation with androgens, or estrogens, or both, for the temporary control of breast cancer. Then, as a sequel to the sinking of a naval vessel that was laden with mustard gas in 1942, the pharmacologist Gilman recognized the significance of the pancytopenic action of the sulfur mustards on the exposed American sailors. This led to the landmark screening programs of the United States Army Chemical Warfare Service, which culminated in 1945 with the development of the nitrogen mustards or alkylating agents, capable of inducing rapid transient inhibition of diverse human and animal lymphoid tumors.

The next major advance came in 1947 when the vitamin biochemist Subba Row, by a process of serendipity, stumbled onto the nitrogen-substituted derivatives of folic acid. These were provided to his pathologist friend, Sidney Farber, who, having turned clinician, published an enthusiastic report of a supposed tumor inhibitory action of "folic acid substituents." Whether Subba Row's vitamin preparations constituted an impure mixture (eluate) containing some *N*-substituted antivitamin derivatives of folic acid was never clarified. Shortly after this perplexing report, Richard Lewisohn of Mount Sinai showed that material from Subba Row's laboratory did inhibit breast carcinoma in mice, and reticulum-cell sarcoma, temporarily, in at least one famous patient, the home-run king Babe Ruth. At this crucial moment in the history of cancer chemotherapy, Farber was provided with purified *N*-substituted true antagonists of folic acid (i.e., aminopterin and methotrexate), which produced spectacular unprecedented regression of acute leukemia in a small group of children.

These fascinating powerful antagonists of folic acid soon became the focal point for countless studies of the metabolic competition between folic acid and citrovorum factor and their metabolic antagonists. These first antimetabolites, known as "antifols," were hailed throughout the lay and medical press as the harbinger of the long-sought magic bullet against cancer.

By 1950 it appeared to the laity and to the clinical onlooker that the basis

for a rational approach to chemotherapy had been provided by a series of unexpected discoveries. The many new drugs that seemed so promising appeared to justify the customary hopeful prediction at the annual Cancer Association meetings that the cancer problem would be solved in just a few more years. In rapid succession, the carbamate inhibitor urethane, an orally effective nitrogen mustard (triethylenemelamine, TEM), and a long-acting parenteral carrier form of nitrogen mustard (thiophosphoramide, Thio-TEPA) came along. The temporary control of lymphoid cancers by these agents provided much respect for the field of cancer chemotherapy as well as a tremendous stimulus for vast amounts of research and clinical investigation of new drugs. The first decade of cancer chemotherapy (1945–1955) ended with high hopes among the then relatively small group of workers in the field. The cancer chemotherapists had by that time assumed a respectability and developed a *raison d'être.*

Then the unexpected happened! Antibiotics rapidly vanquished most of the important infectious diseases, and polio and tuberculosis were virtually controlled by giant strides in immunotherapy and chemotherapy. Consequently, the public suddenly became aware of the tremendous increase in both the relative and absolute incidence of cancer deaths, particularly when brought to its attention by highly publicized deaths of a succession of outstanding celebrities and public officials. The spectacular synthesis of a fraudulent antipyrimidine, 5-fluorouracil, from the chemist's drawing board by Heidelberger seemed to point the way to the single magic bullet. The field of cancer chemotherapy became the province of the newspaper reporter, the magazine sensationalist, and the emotionally involved laity. The public reacted by becoming oversold on the prospects for an early cure of cancer by means of chemotherapeutic agents. Chemotherapy, dubbed the Cinderella of medicine, was showered with an embarrassing and expanding pocketbook that became the envy of basic scientists in other fields. The concept was freely advocated that if enough men and money were concentrated on the effort, a quick and ready solution to the problem of incurable advanced cancer would be found. By 1968, we had reached a peak expenditure in the United States of almost $450 million per year in cancer research, much of it for chemotherapy research. Fifty thousand compounds per year had been undergoing testing in the animal and tissue culture screens. Where has all this activity led us now?

The immediate dilemma of the animal chemotherapist is that he suffers from an overabundance of potential tumor-inhibitory compounds. From a total of 600,000 compounds, at least 6,000 so-called positive, i.e., tumor-inhibitory, compounds are available from the extensive screening programs of the National Cancer Chemotherapy Service Center and private industry. Most of these compounds are highly toxic even in small animals. When tested in larger mammals, before reaching the clinical level, their toxicity becomes relatively more enhanced than does their antitumor effect. Thus,

the high therapeutic index in mice rapidly narrows as these compounds are tested in progressively larger tumor-bearing mammals. To make an adequate study of the pharmacology and toxicity of only one of these several thousand positive compounds in animals and to screen against a broad spectrum of experimental and human tumors is a difficult, tedious, and expensive endeavor. Each compound so tested would represent an investment of at least a half-million dollars and several years of work. Relatively few of the positive compounds have reached the earliest, phase I, clinical trial in man or could be expected to in the near future. It is fair to state that less than 75 compounds have been comprehensively studied in human clinical trials (phase II) since the start of chemotherapy research in the United States.

It is no wonder, therefore, that the validity of the national cancer chemotherapy program has become a constant source of controversy among noncancer research biologists. Many biologists believe that the answer to the cancer problem will elude us until the mechanisms of the sudden change in tumor growth, dissemination, regression, and immunity are better understood. Clinical chemotherapists, in reply, point to the success of current drug combinations that are already being used to cure patients with certain types of heretofore fatal neoplasms. Moreover, the triumphs of nonneoplastic chemotherapy are obvious, as in the recent control of tuberculosis by drug combinations and even of diseases of unknown cause in the past—such as malaria, against which it was possible to develop an effective, albeit imperfect therapeutic agent (quinine) capable of saving millions of lives for 400 years before the cause of malaria became known.

The clinician and family involved with the patient with advancing cancer cannot wait for a full understanding of the biochemistry of cancer. They are in a position that is very much analogous to that of the homeowner trying to eliminate crabgrass from his lawn. When only one or two different types of herbicide were available 15 years ago, homeowners found that they either overdosed the lawn with these single chemicals, thereby killing the desirable grasses, or failed to obtain the necessary effect by following homeopathic policies of underdosage. These crabgrass killers were often administered too early or too late for optimum effects. Now, by a series of carefully and sequentially applied combinations of herbicides beginning early in the pregermination phase and ending shortly before the undesirable growth attains maturity, it is possible to completely eliminate the undesirable growth. Only two steps are really necessary for the herbicidal (chemo) therapist at present.

1. To follow rigidly the directions of the manufacturer, the result of many years of trial and error
2. To welcome the intervention of the winter season that allows certain natural and nutritional (immunological) factors to favor the growth of normal grass (cells)

The clinician would like to have the fortuitous intervention of a dormant (winter) season in his attempts to control clinical cancer. He must abandon the forlorn hope of the single magic curative bullet. He can use a meager armamentarium of 50 agents available for individual, sequential, or combined use with a number of hematostimulative anabolic and immunological adjuvants. These agents result in transient, worthwhile clinical palliation, which may at times be so spectacular as to represent the "near breakthrough" that the family may have been led to expect soon. Incredulity, utter despair, and frustration replace euphoria sooner or later. This two-edged sword becomes the bane of existence for both the chemotherapist and the patient's family. Yet, since the careful use of combinations of different chemotherapeutic agents has made it possible to cure certain animal tumors heretofore incurable after single drug treatment, it seems realistic to expect an increasing incidence of clinical cures. These have already been achieved in such human tumors as choriocarcinoma in the female, acute lymphoid leukemia and Wilms' tumors in children, and seminoma in the male. Hodgkin's disease may be approaching this category. A virtual cure (5 to 10 years of normal survival) may soon be demonstrated in a small percentage of such not-uncommon neoplasms as lymphosarcomas, reticulum-cell sarcomas and myosarcomas, and multiple myelomas. As cancer control through the use of drugs becomes more successful for more patients, the problem of secondary and tertiary cancers will arise.

Although hopes for inducing cure of the more common forms of human cancer through chemotherapy are thus not purely speculative, the realistic near-term objective now is to add 1 to 3 years of control and to increase survival with double and triple combinations and sequential cytotoxic chemotherapy to delay tumor resistance in the common carcinomas of the breast, ovary, endometrium, and gastrointestinal tract.

Much remains to be elucidated regarding the mechanisms of action of effective drugs and the best way to achieve maximum current "mileage" out of them in each individual patient. Although skepticism has been voiced over the contributions offered by uncontrolled small-scale retrospective clinical reports of former years, as compared with recent prospective statistically controlled protocol studies, the case against individual selection and dose adjustment ("custom tailoring") has not been disproven. Critical analysis of large-scale prospective studies reveals much inherent error in planning dose regimens and drug sequences. Interpretation of the significance of results has been at times misleading, particularly if results are advocated arbitrarily as the guide for an optimum therapy among heterogenous, poorly stratified patients with solid (nonleukemic) neoplasms.

Workers in the field should expect solid, slow advancement by the steady introduction of new chemicals with different mechanisms of action. The recent revival of immunotherapy, as an adjuvant to chemotherapy *after a reduction of the tumor load by chemotherapy or before a large internal*

tumor load develops, has sparked a broad public interest (and publicity) in the promises and problems of immunotherapy. As yet, immunotherapy must prove its role in the control of disseminated cancer. Let us hope that it will not turn into a will o' the wisp.

This book aims to distill for the clinician the enormous amount of confusing data that provide a background for the clinical use of the existing drugs and to afford some guide to the current claims for the newer agents or combinations that are continuously heralded by the medical and paramedical press.

This is not a compendium of oncological knowledge, a review of the chemotherapy literature, a comprehensive pharmacological text, or a recipe book. Some of my colleagues in the field of oncology may have reservations about the empirical orientation of this clinical publication. Practicing physicians all over the world who are confronted daily with innumerable patients suffering from advancing cancer require a pragmatic operational evaluation of chemotherapy. We hope hereby to provide cues and guidelines that may help them to achieve the significant worthwhile palliation, albeit transient, obtainable now among a growing list of neoplasms effectively suppressed by modern chemotherapy.

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Ezra M. Greenspan

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Chapter 1

The Empirical Basis for Combination and Sequential Chemotherapy

Ezra M. Greenspan

Clinical cancer chemotherapy has been based on a demonstrated therapeutic potential of each drug for one or more animal tumors in the extensive mouse and rat transplantable experimental tumor "screen." Verification of this tumor inhibition in larger tumor-bearing animals or in spontaneous tumors has not always been achieved before proceeding to human neoplasms. Major biological factors in cancer chemotherapy consist of (a) character of drug toxicity; (b) therapeutic index; (c) optimum time, dosage, route, and schedule of drug administration for maximum host survival; (d) antitumor spectrum; (e) tumor resistance; (f) cross-resistance; (g) potentiation between agents; (h) mechanism of intracellular action (kinetics). The clinician employing these agents should always assess these factors, which may change in a constantly varying host-tumor relationship in individual patients.

TOXICITY

Some general concepts apply to the toxicity of agents available for clinical chemotherapy; the clinical toxicity of individual agents is discussed in Chapter 3.

The near-lethal toxicity induced by cancericidal agents is usually characterized by severe cytotoxic injury to the most sensitive host organs. These almost invariably include the most rapidly proliferating tissues of the bone marrow, the upper gastrointestinal tract, the ovaries, the testes, and the reticuloendothelial system. Yet some newer agents show predictable selective toxicity to the heart, lungs, or central nervous system. Unnecessarily large toxic doses of alkylating agents (thio-TEPA, Cytoxan®, or chlorambucil), antimetabolites (methotrexate or 5-fluorouracil), and other agents such as vinblastine, vincristine, adriamycin, CCNU, and actinomycin D can clearly destroy all normal blood-forming elements. However, an exceptional agent such as bleomycin usually does not inhibit the hematopoietic system even at the highest toxic doses.

The sequence of action of cytotoxic drugs varies, not only on the sensitive organs but especially on the individual hematopoietic elements. Major

significant differences occur at safe, low doses in the therapeutic range. Therefore, different characteristic warning signs of impending toxic effects on the hematopoietic system can be expected to appear in sufficient time to permit prompt interruption of drug therapy, reconsideration of dosage or protective measures. Although undue toxicity should be avoided, *tolerable toxicity is often desirable* since it is often the *sine qua non* of an effective antitumor dosage. The pitfall of homeopathic underdosage should be avoided to achieve optimum therapy. Detailed knowledge and experience with the sequence, timing, and toxicity of each drug on the hematopoietic system are essential for its optimum safe administration. The common alkylating agents differ markedly in their sequence of toxicity as do the antimetabolites. For example, the rapidly acting nitrogen mustard, Mustargen®, should be expected to depress all marrow elements 7 to 10 days after administration, whereas thio-TEPA may selectively depress the platelets to dangerous levels, but not before 3 to 4 weeks have elapsed after starting the priming dosage, and at times there is no significant anemia or leukopenia. The nitrosoureas (BCNU, CCNU, methyl-CCNU) often produce delayed pancytopenias as late as 4 to 8 weeks after administration. In contrast, Cytoxan® can be given in platelet-sparing dosage, which selectively suppresses the white count early in the course of its toxic action, 10 to 14 days from onset. Cyclical schedules of Cytoxan® are compatible with a normal hemoglobin and platelet count despite the induction of a recurrent leukopenia and a cyclic alopecia. The platelet count actually may increase with the acute mitotic inhibitors, the (periwinkle) vinca alkaloids, Velban® and vincristine, with or without the appearance of leukopenia or anemia. However, if dosage of all alkylating agents, antimetabolites, and vinca alkaloids is exceeded beyond the minimum necessary to suppress one of the hematopoietic elements initially, a panmyelo-suppressive effect on all hematopoietic elements could be expected. This is notoriously true of both the slow-acting nitrosoureas (CCNU, BCNU, methyl-CCNU) and the fast-acting adriamycin and daunorubicin. The optimum effective dosage in cancer chemotherapy is usually indicated by an early minimal selective leukopenia without thrombopenia or anemia.

The clinical occurrence of hematopoietic toxicity is additionally complicated by the fact that the same drug in patients with diverse neoplasms at different ages often exhibits a different sequence and dosage necessary to induce hematopoietic toxicity. Higher doses may be needed in some carcinoma patients to induce toxicity equivalent to that seen at lower doses in lymphoma patients. Methotrexate given alone can induce stomatitis in patients with carcinoma or sarcoma before any sign of hematopoietic toxicity becomes apparent. By contrast, severe bone marrow damage will usually develop in patients with leukemia or lymphoma if methotrexate is given until the appearance of stomatitis. The reputation of methotrexate as an inducer of aplastic anemia has been caused, in part, by ill-advised attempts

to monitor methotrexate dosage by the appearance of stomatitis in leukemia or lymphoma patients with unusually sensitive bone marrows. Severe bone marrow damage from most agents should be expected in leukemia-lymphoma patients at an aggregate dose much less than that required in equivalent solid tumor patients.

Substantially lower dosage given to patients in poor medical condition usually will induce toxicity comparable with much higher dosage in patients in good medical condition. A 40 to 50% reduction of dosage of most agents is usually required for safe therapy in older patients (over 65 to 70 years of age). A large reduction in vinca alkaloid dosage is therefore necessary to avoid severe neuropathy in the aged. Fluorouracil pushed beyond the occurrence of diarrhea to leukopenia can result in unnecessary fatality, especially in the aged. Kidney function may be paramount in assessing safe dosage of some agents. Toxicity and safe effective dosage thus cannot be predicated alone on any rote factor based on body surface or weight, but must be critically and individually adjusted according to the pretreatment-predicated clinical risk category (Table 1–1) of the patient, and later by the observed tolerance of the given dosage in each patient.

Another important aspect of clinical toxicity involves the distinction between tolerable toxicity and intolerable toxicity. The same toxic action in one type of cancer patient may be tolerable, but in another patient completely intolerable. For example, neuropathic ileus resulting from high doses of vincristine may be a tolerable side effect in a good-risk patient with lymphoma, but it is a fatal side effect in a patient on the verge of intestinal obstruction from ovarian or gastrointestinal abdominal carcinomatosis. Certain amounts of nausea, vomiting, or diarrhea may be annoying but of no major clinical significance in good-risk patients receiving agents such as

TABLE 1–1. *Poor-risk category for chemotherapy*

Extensive X-ray therapy to bones
Recent marrow suppression by drugs
Diffuse osseous metastases
Impaired renal function
Marked anemia, hypoproteinemia
Protracted vomiting, diarrhea
Cachexia
Prolonged therapy
i.v. fluids
Antibiotics
Corticosteroids
Diuretics
Hypophysectomy
Adrenalectomy
Age over 65
Mental depression and/or poor rapport

methotrexate or Cytoxan. However, similar gastrointestinal side effects, especially if they occur earlier than expected (e.g., 3 days after onset of 5-FU priming dosage), could represent an ominous sign in both good- and bad-risk patients. Consistent injury to the heart, kidneys, lung, brain, or liver interdicts the usefulness of many potential experimental agents. Yet even these organs can be at some risk provided there is strict adherence to the aggregate cumulative dosage limits of any especially promising agent for the individual case. Fatal pulmonary fibrosis from bleomycin and cardiac toxicity from adriamycin are to be avoided, but palliation may be achievable nevertheless by the careful restriction of the total cumulative dosage of these agents.

The chemotherapist is always faced with different sequences of effect on different tissues when treating diverse neoplasms in changing individuals who may also show a pertinent change in organ metastatic pattern during the treatment itself. The clinical control of the toxicity of anticancer compounds remains at the core of the problem of their safe, effective use. Much clinical experience is required before these agents can be safely employed. The risk category of the patient, based on many clinical features, can be established ideally only by the trained internist-oncologist-chemotherapist who has personally examined the patient at the bedside or clinic, and who frequently observes his changing status.

It is reactionary for the clinician to refuse to use anticancer drugs because they are "toxic." His task is to employ those palliative agents that offer a worthwhile prolongation of life at the expense of tolerable toxicity. The management of cancer patients with chemotherapy involves the maintenance of fluctuating toxic cycles whereby the optimum antitumor action and the maximum survival can be achieved under the close supervision of the specially trained medical oncologist.

THERAPEUTIC INDEX

The established cytotoxic anticancer agents (except hormones) manifest a narrow therapeutic range between the minimum effective dose (MED) and the maximum tolerated dose (MTD) in man. Therapeutic indices (MTD/MED) appear favorable in the small tumor-bearing rodents, which show a 5- to 10-fold range between the minimum effective and the maximum dosage against experimental lymphomas treated with nitrogen mustard (methyl-bis), chlorambucil, vinblastine, and other agents. This wide therapeutic index narrows inexorably as these drugs are tested on progressively larger tumor-bearing animals. The therapeutic index in man, usually less than 3, may become so narrow as to be almost undetectable. For example, 70% of the maximum tolerated dose of vincristine may be necessary to induce a therapeutic effect. Should the dose be increased 20 to 40% above