Design of Cancer Chemotherapy

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Design of Cancer Chemotherapy

Experimental and Clinical Approaches

Volume Editors
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Stemming from the early achievements of 25 years ago, cancer chemotherapy has provided effective means to treat several types of neoplastic diseases.
Progress can be recognized both in terms of the alternatives available in treating patients with a specific tumor type, or with a tumor at a specific stage, and in terms of the number of disease types for which useful treatments can be instituted. For instance, in the case of Hodgkin's lymphoma, Burkitt lymphoma, Wilms' tumors, choriocarcinoma in women, acute lymphocytic leukemia and certain types of skin tumors, a number of patients are free of detectable disease 5 years or longer after having been brought into complete remission by therapeutic means. A major impulse towards achieving this measure of success has undoubtedly come from the use of drugs in multiple combinations, an approach which is further being explored. The use of chemotherapy in combination with other modalities of treatment, particularly X-ray irradiation and surgery, further increases the opportunities for tumor eradication and the spectrum of tumor types for which so-called curative treatments may be realistically designed. Despite the progress achieved, major limitations still need to be overcome before chemotherapy by itself can be generally used as a definitive treatment of cancer. With disseminated diseases, this type of treatment may be the only alternative, especially if included within its scope are both antitumor drugs and agents capable of modifying favorably the response of the host against the tumor. The limitations of the available anticancer drugs are essentially related to the fact that most of them are also toxic to normal tissues and usually show insufficient selectivity of antitumor action. As a consequence, even a relatively minor degree of insensitivity or resistance cannot be overcome by increasing drug doses without incurring unacceptable toxicity. Although some of the agents capable of increasing the defenses of the host against tumor are likely to be more specific in their antitumor action than the cytoreductive drugs available, and thus less toxic to normal tissues, most of them are relatively ineffective against large tumor masses. Consequently these agents are likely to find their maximal utility for disease eradication only when the tumor masses are reduced by cytoreductive treatments. Continuing efforts must therefore be directed towards improving the means and modalities of cancer chemotherapy. It is hoped that one day the significant achievements of the past 25 years will be recognized as representing in retrospect only a beginning. Current approaches towards the design of new and better treatments for cancer have evolved from past experiences and include essentially four major areas, namely: (1) the development of new drugs and therapeutic agents; (2) the design of new treatments with available drugs; (3) the development of new treatment modalities, and (4) the design of ad hoc 'tailored'
treatments for individual patients.
The development of new agents is still essentially empirical in nature but is being increasingly guided by knowledge on the mechanism of action of available drugs and on the characteristics of newly identified cellular targets of potential therapeutic intervention.
The design of new treatments with available drugs is directed towards the identification of new sensitive tumors and towards the development of new combination therapies. The example provided by methotrexate clearly indicates that novel and improved uses of old drugs may lead to their effective utilization in the treatment of tumor types previously not necessarily identified as sensitive targets. Combination chemotherapy has been largely based on the assumption that two or more active drugs combined would achieve increased total effective antitumor drugs dose, especially when the dose-limiting toxicities are different for the drugs combined, and would minimize the selection or development of resistant tumor cell subpopulations. While this approach is being pursued further, new leads are being followed towards increasing the selectivity of action of effective drugs through combinations with other compounds not necessarily active against tumor by themselves. Some of these combinants are intended to modify the pharmacology of the effective drug through such mechanisms as increased activation, decreased inactivation, or increased uptake in target tumor cells. Other combinants are intended to modify the metabolism of tumor and/or normal tissues so as to favor drug effectiveness in tumor cells and/or reduce drug effectiveness in normal cells. Both of these approaches are dependent on the availability of basic information on the pharmacological and biochemical determinants of the antitumor selectivity of the effective drug to be improved through such combinations.
The development of new treatment modalities includes such diversified approaches as the design of drug regimens based on pharmacodynamic and cytokinetic parameters, the application of new types of systemic (e.g. drugs encapsulated in liposomes) or regional drug administrations aimed at increasing the concentration of drugs at the target tumor site, and the development of new modalities based on favorable modifications of the interactions between tumor and host.
The traditional approach in clinical cancer chemotherapy has been to identify drugs and drug combinations which have shown activity against the tumor type of the patient to be treated and to use them also in that patient. This approach is often disappointing due to the fact that usually only a certain percentage of patients with a given tumor type respond to such 'treatments
of choice’. A more recent conceptual approach attempts to predict the specific sensitivity of the tumor of each patient and to treat that patient with individually designed chemotherapy. Such an approach is in its infancy and may ultimately prove to be logistically impracticable. However, its appeal is such that it is well worth pursuing to verify its validity. It is likely that the selectivity of antitumor action of anticancer drugs depends on a multiplicity of factors such as drug uptake and activation in cells, regulatory mechanisms at the proximal site of action, the cascade of metabolic effects resulting from initial drug-induced perturbations, the metabolic requirements of the target cell at the time of drug exposure, and other factors. Taking into account this hypothesis, it is intuitively understandable how non-specific antiproliferative and cytotoxic agents may in fact exert selective effects on a tumor and may provide beneficial therapeutic effects in some patients but not in others with a given tumor type. It would seem important, therefore, to identify a minimum set of biochemical and pharmacological determinants of the antitumor action of drugs that, if measured in patients, might form the basis for the design of ad hoc individualized chemotherapy.

As may be deduced from the above considerations, the development of new drugs and treatments according to the approaches mentioned is largely dependent on: (a) the availability of predictive model test systems in animals which would correctly identify potential activities in humans; (b) the acquisition of further knowledge on the mode of selective action of available drugs in animals and in humans which would aid in the design of better drugs and treatments, and (c) the implementation of new ideas identifying new targets for therapeutic intervention. Four workshops were organized under the aegis of the International Union Against Cancer (UICC) to discuss selected topics mainly related to the first two of these three areas of importance for the design of new therapies. The first of these workshops was held in Budapest in 1974 [334a] and was focused primarily on a discussion of test systems with particular emphasis on the development of new models utilizing human tumor cells. The second workshop was held in Bratislava in 1975 [334b] and was concerned primarily with a discussion of the mode of action of the major classes of anticancer drugs, with emphasis on the identification of the determinants of the selectivity of antitumor drug action in animals and in humans. The third workshop was held in Moscow in 1976 [334c] and was concerned primarily with the identification of biochemical and pharmacological determinants of drug action in solid tumors in humans as a possible basis for the prediction of drug action in individual patients and the problems related to tumor sampling. The fourth workshop was held in Buffalo, New York in
1978 and was concerned primarily with the heterogeneity of tumor cell populations and with ways to overcome the problems this heterogeneity poses in connection with the identification of biochemical and pharmacological determinants of drug action in target tumors. In this volume, the topics considered in those workshops are represented by a selected group of chapters, where the issues raised at the workshops are discussed in the light of current progress. The first part of the volume is concerned primarily with model test systems and their potential role in chemotherapy, the second part deals with the identification of biochemical and pharmacological determinants of the action of certain classes of anticancer drugs and the third part outlines problems and current approaches in the separation of cell subpopulations from an heterogeneous tumor cell population. These are three major areas of concern in current attempts to develop new types of anticancer drugs and to design new treatments, including possibly treatments designed to fit the prerequisites for response of individual patients.