ORGAN DIRECTED TOXICITIES OF ANTICANCER DRUGS

edited by
Miles P. Hacker
John S. Lazo
Thomas R. Tritton

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PREFACE

The addition of chemotherapy as an effective means to treat cancer has had a major impact on selected human malignancies. Due to a general inability to differentiate between normal and neoplastic cells, little selectivity exists in currently used oncolytic drugs. Consequently, significant toxicity to the patient is expected when systemic cancer chemotherapy is chosen as an appropriate therapeutic intervention. Much of this toxicity, such as damage to the bone marrow, gastrointestinal tract, or hair follicles, is predictable based upon the fact that anticancer drugs kill actively dividing cells. These types of toxicities, while serious, are usually manageable and reversible and are, therefore, not often considered to be dose limiting.

Unfortunately, several of the most important anticancer drugs also damage tissues in which the growth fraction is relatively small. Such toxicities can not be predicted based on the chemical structure of the drugs, are often not detected in preclinical studies, and are encountered frequently for the first time in clinical studies. Further, unlike most of the proliferative-dependent toxicities, the unpredicted toxicities are usually irreversible or only partially reversible upon cessation of drug administration. Because of this, the unpredicted toxicities are referred to as dose limiting. They represent a significant barrier to the ultimate efficacy of several of our most important anticancer drugs.

Significant research effort has been directed toward developing a better understanding of the mechanisms of such dose limiting toxicities. For some drugs, this knowledge has resulted in clinically effective ways to diminish specific toxicities. In others, no such inroads have been made. In spite of the clinical importance and the extent of research expended to date, no symposium had been convened at which investigators from various disciplines could meet to discuss research observations and concepts. Recognizing this, the First International Symposium on Organ Directed Toxicities of Anticancer Drugs was convened by the Vermont Regional Cancer Center in Burlington, Vermont on June 4-6, 1987. In order to provide focus to this meeting, the organizers chose to concentrate on the heart, lung and kidney as the sites of dose limiting toxicities.

This volume includes the manuscripts of the invited speakers from each of the three sessions. Mechanisms of toxicities and approaches to diminishing toxicities of each of the organs mentioned above are described. The speakers were requested to review recent developments and to highlight new areas of focus and promise. The abstracts of the scientific posters that were presented at the symposium are also included.

The editors wish to thank the contributors for their timely presentations and manuscript preparation. Obviously, this symposium would not have been possible were it not for financial support provided by several sources as acknowledged elsewhere in this volume. The conveners gratefully appreciate this support. Special thanks are also reserved for Joan MacKenzie and Maureen Hanagan who, with support of their respective staffs, provided the local arrangements and general organization necessary for the success of the Symposium.

Miles P. Hacker, John S. Lazo and Thomas R. Tritton

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I.H. Krakoff

The Irrelevant Toxicities of Anticancer Drugs

I.H. Krakoff

The origins of cancer chemotherapy are in toxicology. During World War II a unit of the chemical warfare service stationed at the Edgewood Arsenal in Maryland studied poison gases with particular emphasis on the mustards. The unit was headed by Dr. Cornelius P. Rhoads, on leave from his position as Scientific Director of Memorial Hospital. One must assume that in studying the antiproliferative effect of the mustards, Rhoads and his colleagues were, from the beginning, keenly aware of the potential for these compounds as anticancer agents. The animal studies conducted at the Edgewood Arsenal provided a background on which those investigators were able to build, with the major military disaster at Bari, Italy, providing an opportunity to study the toxic effects of nitrogen mustard in a large number of human subjects. During the same period of time a few patients with lymphoma were treated at New Haven with nitrogen mustard and enjoyed dramatic, although brief, remission in their disease. By the end of the war it was clear that a potent agent with significant potential for use as an anticancer drug had been developed.

Toxicity is one of the major problems in the development and use of anticancer compounds.

A more accurate term might be selectivity; since toxicity to tumor cells is the aim of cancer chemotherapy our search is not for non-toxic compounds but rather for compounds which will selectively damage tumor cells without damaging normal mammalian cells. That goal has been achieved in antibacterial chemotherapy. The demonstration of antibacterial properties of sulfanilamide in the 1930's was based on the requirement of certain bacteria for para-aminobenzoic acid. Adequate concentrations of sulfanilamide deprived bacteria of PABA. Human cells, not requiring exogenous PABA, were not damaged by sulfanilamide. This exploitable biochemical difference between bacterial cells and mammalian cells does not have a parallel in a difference between normal human cells and human tumor cells. It is this lack of selectivity, or at least the failure to demonstrate the difference to date, that has made it so difficult to develop non-toxic antitumor drugs. In 1941, William Woglom stated "to think of a systemic treatment for cancer would be almost as difficult as to dissolve the left ear and leave the right ear intact." In 1987, although recognizing the inherent logic of that statement, it is clear that exploitation of quantitative differences between tumor and normal cells has provided some tools with which significant antitumor effects can be obtained with acceptable toxicity to the human host.

Most anticancer drugs, as part of their antiproliferative effect, are regularly toxic to those organ systems which are characterized by active proliferation. These include the bone marrow, the gastrointestinal epithelium, hair follicles, germinal epithelium and lymphoid tissues. Less

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