Evaluating New Antineoplastic Agents

The editor interviews Carl G. Baker, M.D., Director, National Cancer Institute, Bethesda, Maryland.

Dr. Holleb
The National Cancer Institute Chemotherapy Program has tested many drugs which show promise in the treatment of certain cancers. Where does the material for testing originate?

Dr. Baker
From a wide spectrum of sources including natural products from plants and animals, antibiotics from bacterial sources, enzymes and simple and complex synthetic compounds. The N.C.I. has tested tens of thousands of drugs provided by hundreds of universities and laboratories across the country.

Dr. Holleb
Evaluating these drugs must be a very complicated procedure. How is the program organized?

Dr. Baker
The program is organized basically in three stages: (1) Screening through animal tumor systems for antineoplastic activity; (2) Pharmacologic and toxicologic work-up through tests in larger animals and pharmaceutical development; (3) Clinical evaluation.

Dr. Holleb
On what basis does a particular drug graduate from Stage 1 to Stage 3?

Dr. Baker
At the start of the program, and to a large extent even now, compounds are selected, screened and clinically investigated largely on an empirical basis.
Agents for possible clinical trial have been selected mainly through screening against transplanted mouse leukemias and there has been good correlation between the effect in these screening systems and the production of remissions in patients with leukemia and other rapidly growing cancers. Animal screens are now being modified to include those slower growing tumors, which may be used to predict activity against the more common, slower growing tumors in man.

**Dr. Holleb**

What are the next steps for a compound that shows promise in one of these screening systems?

**Dr. Baker**

The agent is then studied along three separate lines, simultaneously. The drug is developed pharmaceutically for an acceptable clinical formulation, schedule dependency studies are started in mice (so that clinical trials are begun on a schedule that is potentially optimum) and toxicology studies are done in dogs and monkeys.

**Dr. Holleb**

Has the toxicity in animals been fairly accurate in predicting toxicity in patients?

**Dr. Baker**

Yes, in the past few years. Using this system, which permits us to designate a starting dosage in patients, we have encountered no unmanageable toxicity with the first clinical dose. However, as survival time increases in cancer patients, we will need additional studies of long term toxic effects.

**Dr. Holleb**

After the above preclinical studies are completed is the compound ready for clinical evaluation?

**Dr. Baker**

Not quite. If a compound makes it this far in the program, it is reviewed by the Chemotherapy Program Staff and is run through a series of specially designed decision making questions which are an integral part of a system developed to monitor the progress of each drug through the entire developmental process. If the drug passes this step in the "decision network apparatus," an investigational new drug application is filed with the FDA after which Phase I of the clinical trial begins.

**Dr. Holleb**

How many phases comprise the clinical evaluation, and what do you look for during each phase?

**Dr. Baker**

The clinical trial consists of three phases. Phase I is a cautious study to determine appropriate human dosage and define toxicity. During Phase II we look for antitumor activity, and Phase III is a randomized, prospective trial which compares, in sensitive tumors, the results of the test drug with another agent of known effectiveness.

**Dr. Holleb**

To select patients whose chances of receiving the best possible medical care and who will not be jeopardized by the investigation must present something of a problem.

**Dr. Baker**

Criteria for selecting patients differs for each phase of the trial. Patients are eligible for Phases I and II only when all conventional therapeutic options have been exhausted. By the time a drug reaches Phase III we know a good deal more about its efficacy and toxicity in patients and thus we are able to carry out
large scale studies. These studies are conducted by the Cooperative Clinical Research Program which is composed of experienced clinical investigators who have responsibility for the cure of large numbers of patients from which subjects can be properly chosen to test multiple drugs in multiple tumor types.

**Dr. Holleb**

How do these cooperative groups work?

**Dr. Baker**

The program, organized around a large number of individual cooperative groups, has now grown to include hundreds of physicians and hospital services throughout the country. Each cooperative group, establishing protocols to be followed by all participating investigators, may have from 10 to 60 active studies in progress at one time involving all the phases of clinical evaluation. One group may study as many as 1,000-1,600 new patients each year. Referee pathologists, radiologists and biostatisticians are also closely associated with the design, conduct and analysis of these studies.

**Dr. Holleb**

In other words, these groups use the same guidelines which have been established cooperatively, even though the participants may be at different institutions.

**Dr. Baker**

Exactly, and in this way we eliminate the type of bias which makes it possible for a physician who rejects "poor risk" patients to obtain better results than a physician who accepts them.

**Dr. Holleb**

How many drugs have made it through all these different stages and phases?

**Dr. Baker**

To date over 60 compounds have produced objective regressions in cancer patients. Of these, about two dozen are widely used clinically. In the more rapidly growing tumors, these drugs are producing longer remissions in a larger proportion of patients and, in some patients with certain types of cancer, these drugs appear to have produced cures.

**Dr. Holleb**

Are the reasons for success with the rapidly growing tumors and the lack of it with the more common slow-growing tumors becoming clear?

**Dr. Baker**

They are. Some drugs affect the cell at all stages of division, some during particular steps in the mitotic phases and some only during DNA synthesis. Our most effective drugs are those which act only at certain stages of the cell cycle. In the rapidly growing tumors, where a high proportion of cells are in mitosis, the cells will reach the vulnerable stages more often than cells which divide more slowly. As we understand more about the cell cycle, kinetics of tumor growth, dose-scheduling effect and so on, we may be able to reproduce our success in slower growing tumors.

**Dr. Holleb**

Thank you, Dr. Baker.