New Directions

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Update: New Cancer Therapies

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Considerable progress in the treatment or management of cancer has been made since the passage of the National Cancer Act in 1971. That act created the National Cancer Program which encompasses all activities supported by the National Cancer Institute and cancer-related activities sponsored by bureaus, institutes, and divisions of the National Institutes of Health. This formalized commitment of resources to the eradication of cancer resulted in a dramatic expansion and diversification of experimental approaches to control this dreadful disease. It also has led to great expectations fueled by media over-interpretation of periodic announcements of important discoveries and breakthroughs. However, a number of cancers are now curable, and the survival and quality of life of individuals with incurable cancers have remarkably improved.

While some cancers are curable with surgery alone, or in combination with chemotherapy and/or radiotherapy, these conventional methods of treatment have almost reached their limits of effectiveness with a cure rate of approximately 50 percent. Therefore, the development of new and more effective therapies is crucial if we are to conquer this dreadful disease.

One of the most distinctive, yet disturbing, characteristics of cancer is its propensity to invade or spread (a process called metastasis) to various organs.

While the uncontrolled growth of benign or non-malignant tumors may occasionally be fatal if vital organ functions are impaired, more frequently the principal cause of morbidity and death is due to the spread of the disease from the original or primary site to another healthy location within the body. Therefore, if spreading could be prevented, cancer could be controlled and, for the most part, cured.

The current challenges facing cancer researchers are: (i) to develop therapeutic plans to either prevent cancer from spreading or the growth of secondary tumors following the dissemination of cells from the primary tumor, and (ii) to develop more sensitive methods for the detection of malignant growths long before they become life-threatening or clinically manifested. Cancer researchers are hopeful that the current developments using biological response modifiers, e.g. interferon and interleukin-2, and monoclonal antibodies will be sufficient to meet this challenge.

Articles debating the success of clinical trials utilizing interferon and interleukin-2 appear frequently in major newspapers and magazines. While there are some reasons to be optimistic that these agents will prove to be effective for the treatment of some cancers, e.g. melanoma (a type of skin cancer) and renal cell carcinoma (the most common malignancy of the kidney), there is no justification for their being heralded, in some quarters, as "magic bullets" or "cure-alls" for cancer. Fueled by extravagant claims, on one hand, and skepticism on the other, cancer patients and their families are often confused.

This article will summarize the results of clinical trials utilizing interferon and interleukin-2 so that those facing this disease can better understand the debate and make more intelligent decisions about whether to participate in clinical trials involving the administration of these cancer therapies.

ADOPTIVE IMMUNOTHERAPY. This procedure involves the removal of some of the patient's white blood cells or lymphocytes and treating them with a protein molecule called interleukin-2. This protein belongs to a family of molecules called lymphokines which are made by certain white blood cells in the body. However, as a result of modern techniques in biogenetic engineering, interleukin-2 now can be produced in large quantities for clinical use.

When interleukin-2 is incubated with the patient's white blood cells, it activates a special group of the white blood cells called "killer cells" and makes them much more effective in selectively killing cancer cells. The interleukin-2 or lymphokine-activated "killer cells" are re-infused, along with sufficient new quantities of interleukin-2, to keep the activated "killer cells" dividing in the cancer patient and thus available to kill cancer cells.

The first results with interleukin-2-activated killer cells were spectacular. For example, researchers at the National Cancer Institute reported that they shrunk tumors in 44 percent of the patients with skin, colon, kidney and lung cancers. This was an impressive finding since these cancers are least responsive to chemotherapy. In contrast, ongoing studies at six other research centers, using the same procedure, are reporting response rates between 10 to 20 percent.

Additionally, adoptive immunotherapy is a very complex treatment to administer, and the present treatment regimen can be highly toxic, causing anemia, fever, fluid retention, nausea and respiratory problems. There also have been a number of infections caused by contamination of the white blood cells during treatment with interleukin-2 in the laboratory.

INTERFERON. Interferon, like interleukin-2, is a natural protein product of white blood cells that acts by stimulation of the patient's immune system. A few years ago, it was widely discussed as the new miracle drug for the treatment of cancer, as interleukin-2 is today. Yet the high expectations have been largely unrealized. Interferon is now primarily used to treat a very rare form of cancer call "hairy cell" leukemia. Indeed, it has been shown to reduce the tumor burden in more than 90 percent of patients with this particular cancer. It is also effective against lymphoma (cancer of the lymphoid tissue), but has not proved to be very useful for the treatment of most cancers when administered alone.

Even in the case of "hairy cell" leukemia, the number of complete cures is low and all patients treated still possess residual "hairy cells" in the bone marrow, which suggests that they will eventually relapse. Therefore, it is unlikely that "hairy cell" leukemia will be cured with interferon unless administered in combination with another treatment method.

MONOCLONAL ANTIBODIES. Monoclonal antibodies are highly specific biological agents, created by cell fusion techniques. They have proven to be remarkably versatile tools in many areas of biological research and clinical medicine. Antibodies are proteins produced by white blood cells, called B-lymphocytes, in response to a foreign substance that invades the body.

Antibodies naturally participate in the complex series of events, called the immune response, which comes into play when a person's health is threatened by infectious or foreign agents, such as viruses or bacteria or cancer. Monoclonal antibodies are more highly discriminating than conventional antibodies, hence their effectiveness in differentiating between normal versus cancer cells which may have similar characteristics. Cancer researchers have taken advantage of this high degree of specificity of monoclonal antibodies to selectively kill cancerous cells without harming healthy cells. Most drugs currently used in chemotherapy lack this selectivity.

Monoclonal antibodies are used in a variety of ways in cancer therapy. They can themselves directly attack or kill tumor cells. They can serve as vehicles for targeting toxic drugs or radioactive substances to tumors. The concept of "targeting" is analogous to a missile (the antibody) which is "armed" with nuclear weapons (the drug or radioactive substance).

By taking advantage of the fact that tumor cells are different from normal healthy cells, one can design a monoclonal antibody "missile system" that can selectively destroy tumor cells. For a cure to be effected, larger doses of drug or radioactivity must be delivered to the tumor than to the surrounding healthy tissue.

In diagnostic radiology, physicians are utilizing monoclonal antibodies to help locate tumor cell masses in the body. Such cancer imaging with monoclonal antibodies constitutes an exciting new approach that is broadly applicable to solid tumors.

In addition, the development of highly purified monoclonal antibodies has made it possible to passively immunize patients against various cancers or other infections. In fact, some researchers are producing "custom-designed" monoclonal antibodies against a specific patient's cancer. This is based on the rationale that cancer is such an individualized disease that even the same cancer is so different in different individuals that individualized therapy may be required.

One of the major problems limiting the clinical usefulness of monoclonal antibody therapy has been the poor expression of antigens (molecules that interact with antibody) unique to human tumor cells. As is often the case, it is the level of expression rather than the absolute absence of an antigen that differentiates tumor cells from normal cells. While technical problems are

Cancer Research At Howard University

The Howard University Cancer Center is the site of some promising research aimed at controlling the spread of cancer. One team of investigators [Kenneth Olden, Sandra L. White and Martin J. Humphries] is attempting to find ways to control cancer by using agents which prevent the spread of cancerous cells through the bloodstream. The potential for therapeutic success of this kind of strategy appears to offer marked improvement over the random, semi-empirical screening approaches used in the past.

Before embarking on their current research project, the investigators considered the following questions:

- Under what circumstances might such agents be utilized for the treatment of cancer patients?
- Will such medication cure the patient or prolong his or her life even though a complete cure is not achieved?
- What chemical and biological characteristics should such drugs have to ensure that they are not toxic to humans, and that they are not rapidly removed or destroyed so that they remain in the body long enough to be effective?
- Are such drugs likely to be effective with minimal impairment in the quality of life?
- Realistically, is the technology available for the commercial production of such drugs at a cost society can afford?

At present, the three Howard researchers are utilizing two experimental approaches to prevent the spread or growth of tumors at secondary sites, such as the lung.

One approach involves the oral administration of a naturally-occurring agent called swainsonine. The investigators have found that swainsonine enhances the capacity of the host immune system to combat cancer. As such, they have classified it as a biological response modifier similar to interferon and interleukin-2.

The second approach involves the injection of a small molecule consisting of five amino acids (glycine-arginine-glycine-aspartic acid-serine) — which is called a pentapeptide — directly into the bloodstream. This specific pentapeptide inhibits the spread or metastasis of cancer by preventing the binding of cancer cells to tissues in the lung. This is important because such binding apparently enables cancerous cells to spread from one organ to another via the blood or other circulating body fluids.

The cancer cells used by the investigators in their experiments had spread to the lungs, but not to other organs in the body. But the investigators found that because binding to the target organ (the lung) is weak or very unstable in the presence of the pentapeptide, the cancer cells could not escape from the bloodstream.

Kenneth Olden (C), **Sandra White** and **Martin Humphries.**

While swainsonine and the pentapeptide affect different steps required for the spread of cancer, both can prevent death caused by the dispersion of cancer to healthy parts of the body. For example, untreated mice died in 21-33 days following the intravenous injection of tumorous cells. But mice injected with tumorous cells *and* administered the pentapeptide showed no signs of lung cancer a year later.

It is therefore anticipated that swainsonine and the pentapeptide will have similar utility when used in humans. The researchers are now engaged in studies to determine if this anticipation is correct. If the two agents *do* prove to be effective in human cancers, the researchers will be ready to initiate clinical trials in patients upon completion of toxicological and pharmacological evaluation of the respective therapeutic agents.

This research is currently supported by grants awarded by the National Cancer Institute of the National Institutes of Health and the American Cancer Society. Articles describing the findings of the Howard research project include those published in the book *Monoclonal Antibodies and Cancer Therapy* (edited by R. Reisfeld and S. Sell, Alan R. Liss, Inc., New York, 1985) as well as recent issues of *Proceedings National Academy of Sciences, Science, Cancer Research,* and *Journal of the National Medical Association.*

The thrust of this particular research, which requires the collaboration of basic scientists and clinicians, is what the authors of the National Cancer Act envisioned as an outgrowth of bringing together individuals from various disciplines into regional comprehensive cancer research centers. Howard's is one of 20 such centers in the United States. □

still associated with the use of monoclonal antibodies in cancer therapy, this experimental approach will likely be useful in virtually all phases of management of the cancer patient.

It is important to realize that the above therapeutic approaches are still highly experimental. However, participation in clinical trials employing these therapies is strongly recommended if one's cancer is known to be unresponsive to traditional treatments or has been diagnosed as incurable.

Clinical trials represent the best treatment that medical science has to offer. However, the physician must consider a number of factors, such as age, general health, type and stage of cancer, and prior treatment before allowing a patient to participate in a clinical trial.

In summary, some new and exciting approaches to the treatment of cancer are currently being developed at several institutions across the country. While several of them show considerable promise, most may have been oversold by the news media, as was interferon a few years ago. Many cancer experts now fear that the recent publicity about interleukin-2 also may not be justified.

In any event, it is unlikely that a single "wonder drug" will cure all cancers. □

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