SYNOPSIS OF THE LECTURE

"Personalized Cancer Therapy: Coming Soon"

Treatment for cancer has always utilized a multi-disciplinary approach including surgery, radiation therapy, and various forms of chemotherapy. Radiation therapy and chemotherapy target the basic cellular proliferation mechanism which often make no distinction between cancer cells and normal cells. Thus toxicity to the normal organ systems by radiation and cytotoxic agents often become the limit of how much can be given to achieve effective control of the cancer.

With the advance of molecular biology and molecular genetics, cancer researchers have been able to identify specific genetic alterations associated with the formation and progression of specific forms of cancer, for example colon cancer, breast cancer, and brain cancer. These specific molecular and genetic alterations are beginning to be used as target for developing specific drugs with the goal that if the drug can eliminate the specific alteration that occur in the cancer cells and not the normal cells, then the drug can eliminate the cancer cells without causing toxicity to the normal organ systems. However, as expected, the neoplastic transformation and maintenance process is a very complicated and often overlapping network of oncogenes and tumor suppressor genes mediating a complex signal system. Not only this is different from one type of cancer to another type of cancer, it is often different from one patient to another patient with the same type of cancer. This brings a challenge to cancer researchers in the laboratory as well as in the clinic, i.e., is it possible to have a therapy plan that is tailor designed for a specific patient with a specific pattern of molecular alterations driving the neoplastic process in that particular patient? It becomes the concept of personalized cancer therapy.

To make personalized cancer therapy work, which we are beginning to see examples of this possibility, several criteria or questions will need to be fulfilled or answered. Using brain cancer, my specialty, as an example:

1. Are there specific genetic alterations occurring in malignant brain tumor that constitute the driving force of the growth and spread of the tumor? The loss of a gene, PTEN, which regulates an important signaling pathway in glioblastoma, the PI3K pathway, and the over expression of a growth factor receptor, epidermal growth factor receptor, have been identified in over 60-70% of patients with glioblastoma.

2. Is the growth of the tumor dependent on these altered signals, genes, or proteins, thus eliminating these targets will provide control to the tumor? The PI3K pathway has been shown to be a critical signaling pathway that regulates cell survival, cell migration, and angiogenesis which constitutes the major neoplastic phenotypes. The more complicated factor here is whether the PI3K pathway is working alone or working in connection with other interesting or interacting pathways.
3. Can these altered signals, genes, or proteins be identified in the tumor sample prior to initiation of therapy? Technological development in the last few years has provided a means to measure the presence of these proteins as well as the activity of these proteins from even a small amount of tumor tissue. Advanced computer technology has also provided a means to develop high throughput ways to identify multiple markers in multiple samples in a timely fashion such that the information can be made available to formulate or design a specific therapy plan.
4. Are there ways to measure the effectiveness of the treatment in an early stage of treatment so as to predict the chance of success of the specific therapy? The development of imaging technology with MRI and PET has brought us into the era of molecular imaging. Through these imaging devices it is possible to have an early assessment of the activity of the specific protein before and after treatment, or the outcome of the treatment effecting the tumor invasion or the tumor vascularization processes. These early observations potentially will allow the doctor to make early decisions to continue or to change the therapy.
5. Can drug, whether chemical or biologic, be made against these proteins or signals? Through the effort of many major pharmaceutical and biotechnology companies, a series of drugs rationally designed and synthesized, or through screening of chemical libraries, has entered into various stages of clinical development, some in fact with very encouraging results.

Therefore, we believe enough advances have been made in the last 5-10 years that "Personalized Cancer Therapy" is indeed possible, not just an idea. There are examples in the clinic that this approach can be done and is beginning to show signs of potential success.