PERSONALIZED, GENOMICS-DRIVEN ONCOLOGY

Reflection on the past and prediction of the future

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About a decade ago, I was an oncology fellow at Yale University when I was asked to see a patient with metastatic gastrointestinal stromal tumor (GIST). I was hoping to find an effective treatment, but the choices were very limited and most drugs did not work for this disease. The patient died shortly after his diagnosis. A year later, I had a patient with a very similar presentation and diagnosis. The timing was different though. During that year, the first targeted treatment was developed for GIST and after the patient was started on imatinib mesylate (Gleevec), his tumor went into remission. It was a wonderful feeling and I knew that I witnessed a historic event. Shortly thereafter, the completion of the human genome project led to a significant amount of new information about the genetic variations between individuals and their cancers.

With the help of advances in molecular genetics and computer technology, we are in the process of developing truly individual or personalized medicine. After learning information about a person's genes, proteins, and environment we can more successfully prevent, diagnose, and treat disease. Understanding the molecular profiles of cancers helps us to fit medical care to each individual patient. There are variations of the same type of cancer in different patients, suggesting that genetic factors play an important role in cancer pathogenesis. In common solid tumors like colon, breast, or pancreatic cancer, there are an average of 33 to 66 genetic mutations. Certain tumor types display many more mutations than average. The International Cancer Genome Consortium (ICGC) has been coordinating a large number of research projects to provide a comprehensive map of the genomic changes present in many forms of cancers. The primary goals of the ICGC are to generate comprehensive catalogues of genomic abnormalities in tumors from 50 different cancers.

Tumors evolve from benign to malignant lesions by acquiring a series of mutations over time. In colon cancer, for example, a mutation in a normal epithelial cell leads to the formation of a small adenoma. This adenoma grows slowly, but a second mutation in another gene unleashes another round of clonal growth, that allows an expansion of cells into cancer. Because of this cascade of events, it is very important to recognize the early steps of cancer formations, and in the case of colon cancer, undergo colonoscopy on a regular basis to prevent a polyp from developing into cancer.

We can recognize a certain subgroup of patients, who are more likely to respond to therapy based on the genetic make-up of their cancer. Unnecessary toxicity of treatment can also be reduced using targeted therapy and utilizing pharmacogenomics. Genetic testing has also been used to identify individuals with inherited mutations. Patients with mutations in the breast cancer susceptibility gene 1 (BRCA1) and breast cancer susceptibility gene 2 (BRCA2) have a significant risk of developing breast cancer and

may choose to take early preventive surgical measures, like prophylactic mastectomy or medical treatment.

The ultimate goal of individualized therapy is to define the disease at the molecular level so that therapy can be directed to the right population of patients. The first successful targeted therapy was imatinib mesylate (Gleevec) for chronic myeloid leukemia and gastrointestinal stromal tumor. This was followed by the approval of trastuzumab (Herceptin) for patients with breast cancer, carrying overexpression of the HER-2 receptor. Lately we have also recognized that colon cancer patients with mutation to KRAS do not respond to the epidermal growth factor receptor (EGFR) inhibitor drugs like cetuximab. Non-small cell lung cancers (NSCLC) with mutations in the kinase domain of EGFR are much more responsive to treatment with erlotinib. This drug also seems to be more effective in never-smoker Asian patients with adenocarcinoma. Patients with BRAF mutated melanomas had dramatic response from vemurafenib. Sometimes we identify the same targets in different cancers, like the anaplastic lymphoma kinase (ALK) rearrangement in small subsets of NSCLC patients.

There is extensive gene expression with subpopulation of cells within a single neoplasm, which likely represent a major challenge to biomarker and drug development. Heterogeneity between primary and metastatic tumor can lead to inappropriate use of targeted therapies; therefore it can be necessary to biopsy the first metastatic site. There is evidence of development of drug resistance that can be related to emergence of secondary mutations leading to change of therapy. We have always encouraged our patients to participate in clinical trials. Research studies became especially important when using genomic profiling helps to select individuals for trials providing the maximum therapeutic benefit.

The sequencing of the first human genome cost more than $2 billion and lasted over a decade. Due to advances of technology, selected mutations known to occur frequently in cancers can be sequenced in a few days for a few hundred dollars nowadays. It is estimated that the number of main genetic aberration in any cancer is typically five or six. Because of the multiplicity of genetic aberrations and the presence of resistant clones, three or more targeted treatments may be necessary to achieve durable clinical responses. Until recently, the clinico-pathological parameters of the patient and their cancer's tumor markers were the indicators for prognosis and tumor aggressiveness. This information also led to therapeutic decision-making. We have recognized that prognostic accuracy can be improved by understanding the molecular basis of the different cancer subtypes. Gene expression profiling has been developed to identify numerous prognostic biomarkers. We can use these profiles to estimate the risk of recurrence in colon cancer or predict the benefit of chemotherapy in breast cancer. Recently I had a patient who presented with multiple bone lesions. Traditional pathologic analysis of the mass confirmed the diagnosis as carcinoma of unknown primary. I was not satisfied with the result and the tissue was sent for genetic analysis and second pathological review. Based on the interpretation of this new data, the diagnosis was changed to sarcoma and I was

able to prescribe the right therapy for the patient.

Although there are still some challenges with these new technologies, the standardization of data collected from genomic clinical research and the acceleration of new targeted drugs led to substantial prolongation of life in some patients with advanced cancers. There is a strong belief that cancer deaths can be reduced by more than 75% in the coming decades but that this reduction will only come about if greater efforts are made toward early detection and prevention in addition to improvement in our treatment modalities.