

Targeted Therapy: The Fast Pace of Progress

*"Oft expectation fails, and most oft there
Where most it promises; and oft it hits
Where hope is coldest, and despair most fits."
— Shakespeare W. All's Well That Ends Well. Act II; scene 1.*

Ever since President Nixon made the improved treatment and cure of cancer a national goal in the December 1971 with the signing of the National Cancer Act,¹ there was a generally held belief that basic scientific discovery regarding the biology of cancer would yield to direct improvement in patient outcomes. Despite the vast improvement in the understanding of the multistep genomic process that leads to malignancy, this knowledge did not appear to lead directly to clinical benefit. The disappointment was all the more, when compared to the astonishingly rapid pace of scientific discovery and treatment in the field of acquired immune deficiency syndrome (AIDS).

Cancers share common universal properties, as described by Hanahan and Weinberg.² Despite the basic similarities between cancers, it is recognized that cancer occurs as a specific multistep process defined by the acquiring of genomic defects. The great variety of genomic abnormalities accounts for the heterogeneity in clinical behavior between cancers. Scientific research has increasingly identified key genetic events critical to specific cancer development.³ Regardless of the increasing scientific knowledge regarding the basic biology underpinning cancer development, there appeared to be an inability to use that increased knowledge for therapeutic benefit. In the last decade, however, that inability seems to have been conquered.

The term *targeted therapy* has been used to describe a new generation of small molecules and monoclonal antibodies that have been rationally designed to inhibit specific signal transduction and transcription pathways that are critical for cancer cell growth and survival. Although the term *targeted therapy* has its critics (what anticancer therapy does *not* have a target?), it has been widely adopted: a literature search reveals that the phrase has been used in more than 400 journal articles — 324 since the beginning of the century. We therefore have used this term as a unifying concept in this issue's review of the clinical progress achieved with these therapies in anatomic site-specific malignancy. Although multidisciplinary tumor groups tend to be organized around the anatomic tumor site, we recognize that, in the future, tumors will be thought of, and grouped together, based on their common genetic defects.

The introduction of molecularly targeted therapies in the treatment of breast cancer are reviewed and put into context by Drs. Hobday and Perez. Since these therapies have been in use in breast cancer for almost a decade, mature phase III data are now available regarding the effectiveness of these therapies in the metastatic and adjuvant setting. The large number of compounds that have been evaluated in clinical trials in this disease are comprehensively and concisely detailed in this manuscript.

Perhaps in part due to the relative ease in obtaining tumor tissue, understanding of the basic underlying biology of hematopoietic malignancies has been more advanced than solid tumors. The identification of attractive antitumor targets and the use of small molecules, antibodies, and radioimmunoconjugates are discussed in two reviews: one covering novel therapies in multiple myeloma, and another discussing recent developments in hematologic malignancies. Dr. Chng and colleagues review the improved basic understanding of the biology of multiple myeloma and how a new class of compounds, with a novel mechanism of action, has shown clinical efficacy for this disease. The startling activity of imatinib (Gleevec) in chronic myelogenous leukemia (CML) can be demonstrated by the fact that hematologic remissions were achieved in phase I testing of the compound in CML in transformation in the initial dose cohorts in phase I testing prior to any grade 3 or greater toxicity was observed. The mechanistic understanding of the drug's activity allowed for a tumor specific phase I study, which is a relatively recent development in clinical study. The advances in both chronic and acute leukemias are reviewed by Dr. Kuriakose.

In the review by Alekshun et al, the clinical importance of two monoclonal antibodies, bevacizumab and cetuximab, in the treatment of advanced colorectal cancer are reviewed. The FDA approved both of these agents in the first quarter of 2004. A minority of patients with advanced stage colorectal cancer can be cured with salvage surgery; a vastly smaller number will be cured with chemotherapy. The large number of new small molecules with a variety of mechanisms of action that are currently undergoing clinical testing in advanced colorectal cancer leads to real hope that a medical cure for advanced disease may be a realized goal within the next decade.

New mechanisms of medical therapies will challenge physicians to skillfully interpret the radiographic responses to therapy; existing standard response criteria

may not be applicable to all tumor groups, especially in the era of novel targeted therapies. Incorporation of functional imaging into response criteria, particularly with cytostatic therapies, will be challenges to clinicians and regulatory authorities as they attempt to measure the efficacy of new treatments. Dr. Hersh and coauthors review the varied radiologic features of gastrointestinal stromal tumors (GISTs). These rare tumors have been defined only in the last decade by shared molecular defects.

Medical therapies were previously considered largely ineffective in central nervous system tumors due to the supposed protective properties of the "blood brain barrier." A greater understanding of the changes that occur in the physiology of the brain in the presence of cancer, in addition to a large number of promising new agents, has given new hope in treating these cancers, which are frequently lethal. Dr. Butowski and colleagues present a systematic review of the wide range of agents that have been evaluated, and they convey the scope of past and ongoing research in the rapidly expanding field of neurooncology.

Recognizing the fast pace of progress that has occurred, and will continue to occur, I can safely say that the authors of these timely reviews will be pleased to know that their manuscripts will be significantly out of date by next year. That being said, we hope that the articles herein will help to provide a concise update to clinicians as to the current status of molecularly targeted therapies.

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References

1. Sporn MB. The war on cancer: a review. *Ann N Y Acad Sci.* 1997;833:137-146.
2. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell.* 2000;100:57-70.
3. Balmain A, Gray J, Ponder B. The genetics and genomics of cancer. *Nat Genet.* 2003;33(suppl):238-244.

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