Commentary (Palesty et al)—Imatinib Mesylate: A Moleculary Targeted Therapy for Gastrointestinal Stromal Tumors

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Dr. Eisenberg has produced an excellent, concise, yet comprehensive review of the evolution of the KIT inhibitor imatinib mesylate (Gleevec) and the preoperative and postoperative treatment dilemmas surrounding mesenchymal gastrointestinal stromal tumors (GISTs), particularly in the face of advanced disease and recurrences. The focus of the article is on the natural history of GISTs, from a molecular and pathobiologic perspective, to clarify the rationale for the use of imatinib.

The author effectively addresses the controversies surrounding imatinib use in the preoperative and postoperative treatment of GISTs, with an emphasis on recurrence in the face of previous surgical extirpation. An elegant discussion of the proposed biologic and genetic mechanisms involved in tumor response and resistance provides insight into the possible scientific and medical trends that may emerge from discoveries in these arenas and the ultimate amalgamation of the bench-to-bedside and bedside-to-bench paradigms. The conclusions drawn with regard to the future of molecularly specific chemotherapeutic agents in cancer therapy are both provocative and insightful.

GIST and Imatinib

Prior to the conception of imatinib, the treatment of GISTs was a frustrating endeavor for both clinician and patient because of the unrelenting and progressive nature of the disease regardless of the therapy used, ie, surgical extirpation, chemotherapy, or radiation. Even when surgery was "successful" (negative margins were achieved using meticulous technique and avoiding intraoperative tumor rupture), the recurrence rate was 40% to 80%, with a median time to recurrence of 1.5 to 2 years.[1,2] Characteristics associated with an increased risk of recurrence include tumor size, location, and mitotic rate.[3] In adjuvant and neoadjuvant trials, imatinib is effective and well-tolerated and is anticipated to emerge as the standard treatment for both primary and recurrent GISTs, either alone, in conjunction with surgery, or as part of a multimodality, target-specific "designer" drug regimen.[4-6]

Imatinib as a Neoadjuvant Agent

Our limited experience with imatinib as a neoadjuvant agent has been extremely rewarding and has certainly decreased the potential morbidities associated with surgery. One elderly, frail patient with a pathologically documented GIST who presented with a complex enterocutaneous fistula and large bulky disease of the small bowel initially received preoperative imatinib. A positron-emission tomography (PET) scan performed 7 days after the initiation of therapy went from grossly positive to essentially nonreactive, with glycolytic activity limited to the periphery of the tumor. At 8 weeks after neoadjuvant therapy, it was apparent intraoperatively that the center of the mass had undergone necrosis. Interestingly, a mesenteric lymph node returned with metastatic disease. The patient continues to take imatinib postoperatively with no side effects.

A second patient presented with a rectal mass that was biopsied and shown to be a GIST. It was felt that she would require an abdominoperineal resection to completely remove her disease. She elected to try imatinib and, after 8 weeks of treatment, the dramatic tumor shrinkage allowed her to undergo a transanal excision with negative margins and preservation of her sphincter. These cases clearly demonstrate the potential utility of neoadjuvant imatinib therapy.
Response, Resistance, and the Search for a Cytotoxic Agent

Although early evidence from clinical trials overwhelmingly points to the effectiveness of imatinib, the previous two cases illustrate some of the unresolved quandaries.[4-6] These dilemmas are addressed thoroughly by Dr. Eisenberg, who further elucidates the oncogenesis of GISTs and investigates the mechanisms responsible for the variety of responses associated with GISTs, as well as their ability to acquire resistance to imatinib.

The discovery that the genetic location of the c-kit mutation is directly correlated to the tumor's responsiveness demonstrates the need for further investigation of targeted therapies to create a lethal, rather than a "static" drug; current evidence suggests that imatinib is more of a "static" than "toxic" drug, as demonstrated by both the varied clinical response times and glycolytic activity on PET.[7-10] Alternative or combination drug therapy targeting the multiple KIT kinase pathways-for example, SU11248- may be a promising temporizing maneuver to overcome resistance to imatinib while searching for a more toxic agent.[11] The focus on cellular targets in the tyrosine kinase pathway reflects a new movement in cancer care. Rather than concentrating on eradication of the disease, many investigators are seeking to control disease progression and prevent drug resistance so that cancer patients may live in symbiosis with their disease.

Dr. Eisenberg is the principle investigator of the Radiation Therapy Oncology Group protocol S-0132, which will focus on collecting and examining tissue from patients with primary and recurrent GISTs, both before and after imatinib treatment. This will facilitate the creation of a large repository of tissue for comparing pre- and posttreatment specimens through an analysis of c-kit, other signaling molecules, and gene mutations, which should help elucidate the biologic effects of imatinib as well as the causes of responsiveness and resistance. The effectiveness of imatinib treatment will be evaluated clinically with PET and 18-fluorodeoxyglucose PET to assess the ability of these techniques to accurately provide information on tumor responsiveness.

Ideally, the findings from this protocol will allow for identification of those patients who will likely respond to imatinib and those who may need treatment with an alternative tyrosine kinase inhibitor. Perhaps patients who will remain progression-free and those who will develop resistance to imatinib can also be identified. This trial's discoveries may assist in predicting the biologic behavior of individual GISTs, allowing for a focused therapeutic plan and, thereby, increasing disease-free and possible overall survival.

Imatinib and the Future of Cancer Therapy

The oncogenesis, evolution, pathobiology, and treatment of GIST are dynamic frontiers of inquiry, with many issues that need clarification before effective control and/or eradication of the disease with rational, cellspecific treatment can ensue. Imatinib and the implications of what has been discovered about its mechanisms have catapulted oncologic research into a new era. The bench-to-bedside paradigm that has been established with the development of imatinib, from initial research in chronic myelogenous leukemia, to its subsequent application to GISTs, has proven the value of working backward.

The ability to identify a specific microbiologic abnormality and design an exclusive therapy for it has shifted the emphasis away from poisoning the entire system with the expectation that malignant cells will be affected. This new model of investigation needs to be transposed into other areas of translational research so that cancer management can effectively progress. Targeted molecular or genetic therapy will eliminate trial and error from this aspect of medicine and transform it from an art into a hard science. Imatinib and its implications are exciting because such therapy may represent the final gateway in the advance toward realizing Ehrlich's "magic bullet" and the dawn of the era of truly useful designer drugs.

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