Commentary (Blanke)—Imatinib Mesylate: A Molecularly Targeted Therapy for Gastrointestinal Stromal Tumors

By Charles D. Blanke, MD, FACP

Molecularly targeted therapy is a hot topic in oncology, and the development of imatinib mesylate (Gleevec) for gastrointestinal stromal tumors (GISTs) is one of our best examples of the successful translation of basic science research into effective treatment of malignancy. Dr. Eisenberg has thoroughly researched the impetus for the use of imatinib in GISTs and has methodically reviewed the results of several completed trials. He broadly discusses mechanisms of resistance to the drug and talks about future directions in GIST research. Dr. Eisenberg has successfully captured much of the early excitement surrounding the success of imatinib, and he appropriately mentions the possibility of applying targeted therapy to other solid tumors.

Of course, it is extremely difficult to comprehensively review a rapidly changing field, and I have no doubt that even this editorial will be out of date by the time it is published. Nonetheless, it is worth supplementing Eisenberg's article with information on some of the most recent (and stimulating) advances in GIST research, in such diverse areas as epidemiology and molecular characterization of response or resistance to imatinib.

Epidemiology Clarified

Eisenberg is correct in pointing out that the older GIST literature was contaminated by the inclusion of other connective tissue tumors, such as leiomyosarcomas. However, Kindblom recently presented the preliminary results of a Swedish population-based study conducted only in patients with confirmed GIST.[1] This trial corroborated the idea that GISTs can arise from any tubular organ of the GI tract (most commonly the stomach), or mesentery and omentum. Kindblom showed that GISTs occur with equal frequency in males and females, and that the age range of patients is large (10-92 years). GIST incidence and prevalence rates were perhaps the most important data to emerge from the study (14.5 and 129 per 1 million inhabitants, respectively), as previous published estimates of incidence varied greatly (< 1 per million to > 36 per million).

Results of Surgery

Eisenberg discusses the poor outcome of patients with completely resected GISTs, but his article might actually understate the poor prognosis of this population. Some series have suggested that only 10% of these potentially cured patients are alive and disease-free at 10 years.[2] DeMatteo and associates have published one of the most thorough data collections, and they included only patients with a confirmed GIST (no patients with leiomyosarcomas or other connectivetissue neoplasms).[3,4] The 5-year disease-specific survival rate for patients rendered free of gross disease was 54%, with a median of 66 months (note that follow-up was much shorter than in the paper referenced above, and that GIST patients can recur long after their resections).

Imatinib in GISTs

Imatinib showed strong evidence of activity in two early trials-the phase II study discussed by Eisenberg and a parallel European phase I/II trial.[5] In the latter, 54% of patients responded, and
another 37% achieved prolonged stable disease. Only 5% had frank progression. Eisenberg mentions a North American Intergroup randomized phase III trial of two doses of imatinib-400 vs 800 mg daily.[6] This trial reported nearly identical response rates for the two doses (49% and 48%, both likely to improve with time and further patient assessment). There were no improvements in progression-free survival or overall survival with the higher dose, although it was significantly more toxic.

An international sarcoma consortium carried out a study testing the identical doses, but preliminary results were slightly different.[7] The higher dose was still more toxic and no advantage in terms of overall survival was associated with that dose. However, the 800-mg/d dose was associated with better progression-free survival. The difference in conclusions could be spurious (a statistical phenomenon), or could be a result of the different populations studied. Longer follow-up might clarify the situation, but for now, most North American sarcomologists recommend using 400 mg/d as initial treatment for metastatic patients, and expediently increasing the dose in the face of a less than desired response.

Other Remaining Questions in GIST

Eisenberg's article nicely discusses recent efforts to elucidate factors associated with response or resistance. To date, imatinib is the only drug proven effective in GIST patients with metastatic disease. However, Eisenberg speculates that future patients will be phenotyped, which will aid in drug selection when additional choices are available. At present, all advanced disease patients who require therapy should be given imatinib, regardless of the presence or absence of KIT or KIT mutational status.[8] We will see if Eisenberg's view of the future is accurate, and whether the GISTimatinib paradigm can be applied to more complex, genetically diverse, and common tumors, such as those arising in the colon, breast, prostate, or lung.

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