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Personalized Therapy: Prognostic Factors in Gastrointestinal Stromal Tumor (GIST)

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Abstract

Over the last decade, considerable progress has been made in gastrointestinal stromal tumor (GIST) with respect to determining prognosis and therapy. Here, we will summarize some of the major developments and how they have led to an increased use of personalized treatment in GIST.

Primary disease

The standard of care for localized, primary GIST is surgical resection. Historically, though, nearly 50% of patients died by 5 years after surgery.[1] The development of the tyrosine kinase inhibitor imatinib mesylate (Gleevec, Novartis Pharmaceuticals) has dramatically improved outcome in metastatic GIST. When it became apparent by the end of 2000 that imatinib is effective in advanced GIST,[2] a randomized trial (American College of Surgeons Oncology Group (ACOSOG) Z9001) was conceived to compare 1 year of adjuvant imatinib to placebo following the resection of primary GIST ≥3 cm. The goal was to prevent or at least delay tumor recurrence. The trial began accrual in 2002 and was stopped prematurely in 2007 by the data safety monitoring board because of the difference in recurrence-free survival (RFS) between the arms. With 20 months of median follow up, the 1 year RFS in the imatinib arm was 98% versus 83% for the placebo arm.[3] These data led to FDA approval of adjuvant imatinib in 2009 and changed the standard of care for primary GIST.

One of the current issues in adjuvant therapy for GIST is which patients should be treated. Outcome in GIST depends on several pathologic variables. Mitotic rate is the predominant predictor of outcome.[4] Tumor size and location (stomach is more favorable than small intestine) are also important, but to a much lesser extent. Based on these 3 variables, Miettinen devised a stratification scheme to identify patients as very low, low, moderate, or high risk of recurrence.[5] Since the Miettinen criteria do not have a time element, we created a nomogram using the same 3 pathologic features to estimate 2 and 5 year RFS after resection of a primary GIST.[6] We developed the nomogram based on our institutional data and validated it in a series of GIST patients from Spain and another cohort from the Mayo Clinic. We recently reported that patients at low risk of recurrence have had so few events so far in the ACOSOG Z9001 trial that adjuvant imatinib therapy may not be indicated (ASCO 2010).

Another important prognostic factor in GIST is the mutation status of the tumor. Patients with a *KIT* exon 11 deletion do worse than those with either an exon 11 point mutation or insertion.[4, 7] Within the exon 11 deletion group, patients with involvement of amino acids

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Conflict of Interest
Dr. DeMatteo has served on advisory boards and received honoraria from Novartis Pharmaceuticals.

557 and/or 558 have worse outcome.[4, 8, 9] How adjuvant imatinib interacts with the prognostic pathologic factors has not been established completely. Patients with an exon 11 mutation do have longer RFS when treated with adjuvant imatinib (ASCO 2010). Meanwhile, patients with a platelet-derived growth factor alpha (*PDGFRA*) D842V mutation are unlikely to benefit from adjuvant imatinib, since there is little activity against this mutation in the metastatic setting.

The optimal duration of adjuvant imatinib has not yet been defined. What is clear is that 1 year of postoperative therapy appears to be insufficient for at least some patients. Notably, the rate of recurrence increased in the ACOSOG Z9001 trial after 18 months (6 months following the prescribed 1 year dose). Results are expected this spring regarding the Scandinavian Sarcoma Group trial (SSGXVIII) of 1 versus 3 years of adjuvant imatinib.

Metastatic disease

Among patients with metastatic GIST in the era prior to tyrosine kinase inhibitors, we found that mitotic rate and tumor size of the *primary tumor* as well as morphology (spindle worse than epithelioid) were prognostic.[10] Imatinib achieves a partial response or stable disease in about 80% of patients with advanced GIST and a median survival of nearly 5 years.[11] Tumor mutation status in metastatic GIST predicts response to imatinib. Patients with a *KIT* exon 11 mutation are more likely to have a partial response and have a longer progression-free survival than those with a *KIT* exon 9 mutation or those without a *KIT* or *PDGFRA* mutation (i.e., wild-type (WT)).[12, 13] Furthermore, high dose imatinib (800 mg/day) achieves a longer PFS in patients with an exon 9 mutation than standard dose imatinib (400 mg/day), but does not affect overall survival.[14]

The median PFS in patients with metastatic GIST who are treated with imatinib is approximately 18 months.[14] The mechanism of resistance in patients with a *KIT* exon 11 mutation is a secondary *KIT* mutation in approximately half of patients.[15-17] Secondary mutations tend to occur in the ATP binding pocket or activation loop, both of which are unusual sites of mutation in untreated GIST. Some secondary mutations are sensitive to sunitinib (e.g., V645A and T670I).[18] Patients who have failed imatinib therapy are more likely to respond to sunitinib maleate (Sutent, Pfizer) if they have a *KIT* exon 9 mutation or WT tumor.[19] If sunitinib fails, a variety of other multi-kinase inhibitors are available (e.g., sorafenib and nilotinib), but not actually FDA approved in GIST. There is a need for new agents that are effective in resistant GIST.

Thus, standard pathologic variables and tumor mutation status are prognostic in primary GIST and are used to select patients for adjuvant therapy. In metastatic GIST, tumor mutation status is predictive of response to tyrosine kinase inhibition. Further molecular definition of patient subsets is likely to increase our current ability to personalize therapy in GIST.

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