EDITORIAL

Defining the Impact of Adjuvant Therapy in Molecularly Defined Subsets of Gastrointestinal Stromal Tumor
From Lumping to Splitting

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In 1998, the modern era of recognizing gastrointestinal stromal tumor (GIST) as a unique entity began, with a report linking *KIT* protein expression and gene mutations to the putative cell of origin for GIST.[1]

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Immunohistochemical detection of the KIT protein provided a tool to distinguish GIST from other types of cancer (particularly leiomyosarcoma). With accurate diagnosis, it became clear that while some cases of metastatic leiomyosarcoma responded to chemotherapy, the response rate of GIST was essentially 0%.[2] Therefore, KIT expression could be used to identify patients with GIST who would not benefit from conventional chemotherapy.

Beyond the world of sarcoma, imatinib therapy began in clinical trials aimed at chronic myeloid leukemia. During early development, imatinib was also found to be a strong inhibitor of KIT kinase activity.[3] Following reports on the efficacy of imatinib for treatment of chronic myeloid leukemia,[4] 2 studies were conducted to explore the activity of imatinib against advanced GIST. Impressively, both studies found high rates of durable single-agent activity, with objective response rates in the range of 30% to 66% and median progression-free survival of 18 to 20 months.[5,6] Correlative science in these early trials identified mutations activating the homologous PDGFRA receptor tyrosine kinase in a minority of GIST cases lacking *KIT* mutations. In subgroup analyses, the highest rate of objective response and the longest relapse-free survival (RFS) were found in patients with *KIT* exon 11–mutant GIST, with inferior responses noted in patients whose GIST had either *KIT* exon 9 mutation or no detectable mutations in either *KIT* or *PDGFRA*.[7]

The success of imatinib treatment in metastatic disease was followed by 2 international phase 3 studies for patients with advanced GIST that compared 2 dose levels of daily imatinib (400 vs 800 mg). Both studies confirmed the extraordinary activity of imatinib for advanced GIST. A meta-analysis combining these trials found similar clinical activity using either dose, except for patients whose GIST harbored a mutation in *KIT* exon 9. This latter subgroup did somewhat better when treated with imatinib at the 800-mg dose level. The meta-analysis also confirmed much less clinical benefit with imatinib for patients with GIST lacking *KIT/PDGFRA* mutations and a total lack of activity in the subgroup of *PDGFRA* D842V-mutant GIST, confirming in vitro studies that showed this mutant kinase variant to be resistant to imatinib.[7,8]

Over the past 16 years, the group of GISTs lacking *KIT* or *PDGFRA* mutations has now been identified to be driven by alternative oncogenic events including loss of succinate dehydrogenase complex or NF1 protein expression, as well as gain-of-function mutations of *RAS*, *BRAF*, or *NTRK3*. Based on our understanding of the characteristics of these GISTs, imatinib treatment may not change the natural history of most (or all) GISTs lacking *KIT*/*PDGFRA* mutations.[9]

As the phase 3 studies for advanced GIST were yielding early results, 2 studies to test the activity of imatinib as adjuvant therapy following resection of primary localized GIST were initiated. The first and largest of these studies was a randomized study of 1 year of imatinib therapy vs placebo for resected GIST (ACOSOG Z9001).[10] This trial demonstrated improved RFS, but no overall survival (OS) benefit, for patients treated with 1 year of adjuvant imatinib, 400 mg daily, compared with placebo. Notably, the rather inclusive eligibility for this study only required that the primary GIST lesion be at least 3 cm in size, irrespective of mitotic index. Thus, many enrolled patients had resected GIST that would now be regarded as having a low risk of recurrence. Biomarker analyses identified that the benefit of 1 year of adjuvant imatinib therapy was confined to patients with *KIT* exon 11–mutant GIST, with no benefit over placebo for other molecularly defined GIST subgroups. To parse even further, within the subgroup of *KIT* exon 11–mutant GIST, patients whose GIST harbored a *KIT* exon 11 deletion mutation had improved RFS compared with point mutations or insertion/tandem duplication mutations in *KIT* exon 11.[11]

To optimize imatinib adjuvant therapy of resected GIST, the Scandinavian Sarcoma Group, along with the German Sarcoma Group, conducted a randomized clinical trial (SSG XVIII/AIO) of imatinib, 400 mg daily, for 1 vs 3 years. In contrast to the Z9001 study, only patients with high-risk GIST were eligible for enrollment. The eligibility criteria for this study included (1) tumor diameter greater than 10 cm or (2) mitotic index of greater than 10 mitoses/50 high-power fields or (3) tumor diameter greater than 5 cm and more than 5 mitoses/50 high-power fields or (4) tumor rupture before or during surgery. Between February 2004 and September 2008, 200 patients were randomly allocated to each duration of treatment. The initial clinical results from this study were reported in 2012 and updated in 2015. In both of these reports, there was superior benefit noted with 3 years of adjuvant imatinib dosing compared with 1 year, in both RFS (hazard ratio 0.60, $P < .001$) and OS (hazard ratio, 0.60; $P = .04$).[12,13]

In their latest update to this study, Joensuu et al[14] report a detailed biomarker analysis of GIST subgroups based on a focused genotyping of the tumors. In agreement with the results from Z9001, patients with a *KIT* exon 11 deletion-mutant GIST derived the most benefit from 3 years of adjuvant imatinib. In addition, these investigators confirmed previous observations that GISTs with *KIT* exon 11 deletions that include codons 557 and 558 have the best outcomes with adjuvant imatinib therapy. The results reported by Joensuu et al[14] are also consistent with previous reports showing that patients with GISTs harboring *KIT* exon 9 mutations, *PDGFRA* D842V mutations, or those lacking mutations in either *KIT* or *PDGFRA* have no discernible benefit with adjuvant imatinib therapy.

How should these data affect clinical practice? In our opinion, physicians who are considering a recommendation of adjuvant therapy for resected primary GIST should first determine the genotype of the patient's tumor. Patients with *PDGFRA* D842V-mutant GIST or whose tumor lacks any *KIT*/*PDGFRA* mutations should not be treated with adjuvant imatinib. In addition, patients with *KIT* exon 9-mutant GIST have not been proven to benefit from the lower standard dose (400 mg/d) of imatinib therapy in the adjuvant setting. Based on the literature from treatment of patients with metastatic disease, it is possible that the RFS of patients with resected *KIT* exon 9-mutant GIST might be improved using higher-dose imatinib therapy (eg, 800 mg/d). Ideally, this approach would be tested in a randomized clinical trial, but the rare incidence of these primary lesions makes such a trial nearly unfeasible. It would be optimal for physicians to discuss these therapeutic limitations and clinically relevant nuances with patients whose GIST has a moderate to high risk of recurrence.

It is clear that patients with *KIT* exon 11-mutant GIST at significant risk of recurrence benefit from at least 3 years of adjuvant therapy. The aforementioned studies demonstrate that most of this benefit is due to the marked improvement in outcomes for GISTs with *KIT* exon 11 deletion mutations (particularly those involving codons 557 and/or 558). However, based on our biochemical understanding of how mutations in *KIT* exon 11 result in constitutive kinase activation and the much smaller numbers of patients with other forms of mutations (eg, point mutations) treated in comparison with the more common *KIT* exon 11 deletion mutation group, we feel that all patients with high-risk GIST and any type of activating *KIT* exon 11 mutation should be offered at least 3 years of adjuvant imatinib.[15] Likewise, we would also recommend that patients with high-risk GIST with imatinib-sensitive *PDGFRA* mutations (eg, those other than D842V) should also be offered at least 3 years of adjuvant imatinib.

What remaining questions are there for adjuvant treatment of GIST? Although the study by Joensuu et al[14] definitively proves that 3 years of adjuvant imatinib therapy is superior to 1 year of therapy, the optimal duration of therapy remains unknown. A limited number of ongoing studies ask whether treatment durations longer than 3 years might yield superior results. In addition, patient selection for adjuvant therapy remains controversial, as Z9001 and SSGXVII/AIO had markedly different eligibility criteria. The SSGXVII/AIO study only included high-risk GIST and showed advantages in both RFS and OS. The Z9001 study included a substantial number of patients with low-risk GIST and reported benefit only in RFS (not OS) using 1 year of therapy. It also remains unclear what lower limit of "recurrence risk" should be used to justify adjuvant therapy in any given individual. Finally, it remains unknown how to best treat GIST lacking *KIT*/*PDGFRA* mutations (eg, succinate dehydrogenase–deficient GIST). As new efficacious treatment options are discovered and developed in the setting of advanced GIST, these treatments should be subsequently tested in the adjuvant setting.

Over the past 16 years, KIT selective kinase inhibitors such as imatinib have revolutionized the treatment of advanced GIST. It is clear that adjuvant therapy with imatinib can improve the RFS and OS of molecularly selected patients with GIST. For these patients, an ounce of prevention may be just what the doctor ordered; for the rest, a pound of research is still recommended.

ARTICLE INFORMATION

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