Ann Surg Oncol (2014) 21:3365–3366
DOI 10.1245/s10434-014-3992-z

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

EDITORIAL – GASTROINTESTINAL ONCOLOGY

Adjuvant Imatinib for GIST: The Pie is Shrinking

Vinod P. Balachandran, MD and Ronald P. DeMatteo, MD, FACS

Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY

The discovery that oncogenic driver mutations in *KIT* and *PDGFRA* are not only causative in gastrointestinal stromal tumors (GIST) but also their Achilles heel has changed the landscape of systemic treatment for solid tumors. The benefit of the tyrosine kinase inhibitor (TKI) imatinib mesylate (Gleevec) in metastatic GIST is now unquestionable. There are 2 phase II and 2 phase III trials that have proven that imatinib extends life, prolonging median overall survival (OS) in advanced GIST from 9 months to more than 5 years.[1–4] Given the remarkable activity of imatinib in metastatic GIST, it was applied in the adjuvant setting. The American College of Surgeons Oncology Group (ACOSOG) sponsored the phase III Z9001 trial comparing adjuvant imatinib to placebo following the complete resection of localized, primary GIST. The trial was stopped prematurely because of a large difference in recurrence-free survival (RFS) between the arms (1 year RFS 98 % on the imatinib arm vs 83 % on the placebo arm; $p < .0001$).[5] Adjuvant imatinib was subsequently approved by the Food and Drug Administration. Recently, we published the long-term results of this trial (median follow-up of 74 months), which has provided additional insight into the optimal use of adjuvant imatinib.[6] The major unresolved issues regarding adjuvant imatinib include (1) which patients should be treated, (2) what are the exact benefits, and (3) what is the optimal duration.

While ACOSOG Z9001 included patients with tumors of at least 3 cm in size, it is now clear that nearly 50 % of the participants had a low risk of tumor recurrence based on tumor size, mitotic rate, and tumor location, according to Miettinen.[7] Just a few percent of low-risk patients developed recurrence, regardless of assignment to the imatinib or placebo arm. Consistent with this observation, more than 70 % of patients appear to be cured by surgery alone based on RFS in the placebo arm.[6] Therefore, almost half of the GIST patients on the trial did not need adjuvant therapy based on risk assessment.

Imatinib response in metastatic GIST depends on the type of tumor mutation. Although the ACOSOG Z9001 was not powered to look at mutation subsets, there are a few notable observations (see supplemental data in Ref. 6). Adjuvant imatinib provided the largest RFS benefit in tumors with a *KIT* exon 11 deletion, which represented 36 % of the patients on the trial.[6] There appeared to be a benefit in *PDGFRA* mutations, but the difference did not reach statistical significance. However, since it has already been established that patients with *PDGFRA* D842V mutations (which comprised about 50 % of all *PDGFRA* mutations) do not respond to imatinib, these patients should no longer be prescribed adjuvant imatinib. RFS in the wild-type tumors (32 patients per arm) overlapped at 1 year and beyond, questioning the role of adjuvant imatinib for these patients. There was slight improvement in RFS at 1 year in the small number of patients with *KIT* exon 11 insertions or *KIT* exon 9 mutations, but not in *KIT* exon 11 point mutations. It is possible that patients with exon 9 mutant tumors may benefit from a higher adjuvant dose, akin to the benefit in the metastatic setting.[8] Data from the Scandinavian Sarcoma Group (SSG) trial examining 1 versus 3 years of adjuvant therapy in predominantly high-risk GISTs support these conclusions, also showing a benefit to longer therapy only in tumors with exon 11 mutations.[9] Characterizing the precise benefit of adjuvant imatinib in patients with moderate and high risk of recurrence by Miettinen, stratified by mutational subtype, is the next step in defining which patients should be treated.

While there is no doubt that adjuvant imatinib increases RFS, the effect on OS is unclear. After a median follow-up of 74 months, the ACOSOG Z9001 trial has not shown a

First Received: 18 July 2014;
Published Online: 14 August 2014

R. P. DeMatteo, MD, FACS
e-mail: dematter@mskcc.org

difference in OS with 1 year of adjuvant imatinib. Meanwhile, the SSG XVIII trial reported an improvement in OS with longer therapy (5-year OS of 92 % in the 3-year imatinib arm vs 81.7 % in the 1-year imatinib arm; $p = .02$). However, the event (i.e., death) rate was quite low at 9 % (37 deaths in 397 patients). Furthermore, there was no difference in disease-specific survival (DSS). After 21 deaths (5 % of 397 patients) from GIST, 5-year DSS was 95.1 % on the 3-year arm vs 88.5 % ($p = .09$). Longer follow-up is needed to resolve whether there is actually a DSS benefit to adjuvant imatinib. As serial radiologic surveillance following surgery for primary GIST has become customary, most patients with recurrence are now identified when they have a minimal amount of disease, which often can be rescued by "crossover" from observation to imatinib. This may prevent showing a difference in DSS with adjuvant therapy.

The optimal duration of adjuvant therapy in GIST remains undefined. The SSG XVIII trial showed that RFS was greater with 3 years of adjuvant imatinib compared with 1 year (5-year RFS 65.6 % in the 3-year imatinib arm vs 47.9 % in the 1-year imatinib arm; $p < .001$), which was consistent with the greater RFS in the imatinib arm after the prescribed 1 year of therapy in ACOSOG Z9001. The PERSIST5 trial is an ongoing phase II trial testing 5 years of adjuvant imatinib therapy in patients at moderate to high risk of recurrence (NCT00867113). For patients at high risk of recurrence, the author's current practice is to discuss the goals of therapy with the patient. If the goal is to increase RFS, realizing that there may not be a difference in DSS, then chronic imatinib therapy is prescribed.

Thus, fewer than half of patients with resected primary GIST $\geq$3 cm should now be considered for adjuvant therapy. The major risk stratification systems can be used to identify patients who have a low likelihood of recurrence in whom adjuvant therapy is not indicated.[7,10] Mutation testing of the tumor should be performed to exclude patients with a *PDGFRA* D842V mutation or wild-type tumor. In the remaining patients, a discussion should ensue about the goals and current results of adjuvant therapy.

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