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Is exon mutation analysis needed for adjuvant treatment of gastrointestinal stromal tumor?

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Abstract

Gastrointestinal stromal tumors (GISTs) are the most common soft tissue sarcoma of the gastrointestinal tract, resulting from an activating mutation of stem cell factor receptor (KIT), and an activating mutation of the homologous platelet-derived growth factor receptor alpha (PDGFRA) kinase. Most GISTs (90%-95%) are KIT-positive. About 5% of GISTs are truly negative for KIT expression. GISTs have been documented to resistant conventional chemotherapeutics. Due to the KIT activation that occurs in the majority of the cases, KIT inhibition is the primary treatment approach in the adjuvant treatment of metastatic GISTs. Imatinib mesylate is an oral agent that is a selective protein tyrosine kinase inhibitor of the KIT protein tyrosine kinase, and it has demonstrated clinical benefit and objective tumor responses in most GIST patients in phase Ⅱ and Ⅲ trials. The presence and the type of KIT or PDGFRA mutation are predictive of response to imatinib therapy in patients with advanced and metastatic disease. Molecular analysis in phase Ⅰ-Ⅱ trials revealed significant differences in objective response, progression-free survival, and overall survival between GISTs with different kinase mutations. The aim of this letter is to touch on the need for exon mutation analysis for adjuvant treatment with imatinib in GIST patients.

Key words: Imatinib; Gastrointestinal stromal tumor; Activating mutation; Stem cell factor receptor; Platelet-derived growth factor receptor alpha; Mutation analysis

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TO THE EDITOR

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract. In general, 75% to 85% of GISTs have an activating mutation of stem cell factor receptor (KIT), 5% to 7% have an activating mutation of the homologous platelet-derived growth factor receptor alpha (PDGFRA) kinase, and approximately 12% to 15% of GISTs do not have a detectable mutation[1-3]. Imatinib mesylate is an oral agent that is a selective tyrosine kinase inhibitor of the KIT, PDGFRA, Abelson (ABL), and ABL activated by fusion with the *BCR* gene tyrosine kinases. Phase Ⅱ and Ⅲ trials have demonstrated that imatinib is effective against metastatic GIST in more than 50% of patients[4-7]. The presence and the type of KIT or PDGFRA

mutation are predictive of response to imatinib therapy in patients with advanced and metastatic disease. Molecular analysis in phase Ⅰ to Ⅱ trials revealed significant differences in objective response, progression-free survival (PFS), and overall survival (OS) between GISTs with different kinase mutations[8]. Previously published studies have shown that the outcomes of patients with KIT exon 11-mutant GIST were better than for patients with KIT exon 9-mutant GIST and tumors without a detectable KIT mutation[1,9]. In a recent trial, Joensuu *et al*[10] reported that in the adjuvant treatment of high risk of recurrence GIST patients, 36 mo of imatinib treatment improved recurrence-free survival (RFS) and OS compared with 12 mo of imatinib treatment. In this study, the KIT exon 11 mutation was found in nearly 65% of both groups. In exon 11 mutation-positive patients, RFS was statistically improved in the 36-mo imatinib treatment group compared with the 12-mo treatment group. However, RFS was not statistically significantly changed in all remaining patients who had a positive mutation other than exon 11, and who had extension of the treatment to 36 mo compared to 12 mo. The presence and the type of KIT or PDGFRA mutation are predictive of response to imatinib treatment. Heinrich *et al*[8] reported that the presence of the KIT exon 11 mutation in advanced GIST patients who were treated with imatinib correlated with improved objective response, time to tumor progression and OS, when compared with the presence of the KIT exon 9 mutation and wild-type genotypes. In the Finnish B2222 trial, assessing imatinib treatment in metastatic GIST patients, the partial response rate was 83.5% for those patients with positive exon 11 mutation, whereas it was 47.8% in exon 9 mutation-positive patients[1].

A randomized European Organisation for Research and Treatment of Cancer phase Ⅲ trial reported that treatment with imatinib 800 mg/d had a significantly superior PFS compared to imatinib 400 mg/d in advanced GIST patients with an exon 9 mutation[11]. Also, Heinrich *et al*[8] reported that imatinib 800 mg/d had improved response rates compared to imatinib 400 mg/d in advanced GIST patients with positive exon 9 mutation. DeMatteo *et al*[12] reported that adjuvant imatinib therapy compared to placebo treatment appears to prolong RFS following the resection of primary GIST, but the effect of mutation on RFS was not reported. On these grounds, the optimal duration of treatment and the optimal dose are not known for operable GIST with a high risk of recurrence, other than for exon 11 mutation patients.

In conclusion, analysis can disclose the type of exon mutation which can be predictive of response to adjuvant imatinib treatment in GIST patients.

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