

Does tumor mutational status correlate with clinical response to imatinib?

Original article Debiec-Rychter M *et al.* (2006) *KIT* mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. *Eur J Cancer* 42: 1093–1103

SYNOPSIS

KEYWORDS gastrointestinal stromal tumor, genotype analysis, imatinib, *KIT*, *PDGFRA*

BACKGROUND

Gastrointestinal stromal tumors (GISTs) frequently harbor mutant *KIT* or *PDGFRA* tyrosine kinases. Imatinib has induced good response rates and improved progression-free and overall survival in patients with advanced GISTs, but it has been suggested that the presence of diverse mutations in different GISTs might cause varying responses to imatinib treatment, and differing resistance profiles.

OBJECTIVE

To investigate the relationship between tumor mutational status and clinical response to imatinib in patients with advanced GISTs.

DESIGN

The analysis used paraffin-embedded tumor blocks collected from patients with GISTs prior to treatment in a phase III cooperative group study. Following pathology review, samples confirmed to be GISTs and yielding sufficient DNA were analyzed for mutations of *KIT* (exons 9, 11, 13 and 17) or *PDGFRA* (exons 12 and 18) using denaturing high performance liquid chromatography and direct sequencing of extracted tumor genomic DNA.

INTERVENTION

Between February 2001 and February 2002, patients with advanced GISTs were randomized to receive a daily dose of imatinib of 400 mg or 800 mg (400 mg twice daily). Crossover was permitted if disease progressed.

OUTCOME MEASURES

The primary outcome measure was progression-free survival, and the secondary outcome measure was overall survival. Response and progression were objectively assessed using RECIST criteria on the basis of the size of the lesions on CT scanning.

RESULTS

KIT mutations were found in 315/377 (83.6%) of the tumors analyzed, including exon 11 mutations in 248 samples (65.8%), exon 9 mutations in 58 samples (15.4%), exon 13 mutations in 6 samples (1.6%) and exon 17 mutations in 3 samples (0.8%). A small number of *PDGFRA* mutations were found, and 52 tumors had no detectable mutations (wild-type). Patients with *KIT* mutations in exon 9 had greatly reduced overall and progression-free survival compared with both those carrying *KIT* exon 11 mutations (with relative increases in risk of death and progression of 190% [$P < 0.0001$] and 171% [$P < 0.0001$], respectively), and those carrying no detectable mutations in *KIT* or *PDGFRA* (relative risk increases of 76% [$P = 0.028$] and 108% [$P < 0.0001$], respectively). After 2 years, the cumulative response to imatinib was 69% in patients with *KIT* exon 11 mutations, 34% in those with *KIT* exon 9 mutations and 25% in those with no mutation. In patients with *KIT* exon 9 mutations, 800 mg/day imatinib was associated with better progression-free survival than 400 mg/day imatinib ($P = 0.0013$), with a 61% reduction in relative risk. In other patients, the response to treatment was independent of dose.

CONCLUSION

Molecular analysis of GISTs is essential to identify patients at high risk of disease progression. The authors recommended imatinib doses of 800 mg/day in patients with *KIT* exon 9 mutations; other patients should start on 400 mg/day, increasing to 800 mg/day in the case of disease progression.

COMMENTARY

Michael C Heinrich*
and Christopher L Corless

GISTs are intra-abdominal sarcomas that respond poorly to conventional chemotherapy. Most GISTs strongly express KIT (CD117), which serves as a convenient diagnostic marker but is also a treatment target. Recent clinical studies with the small molecule KIT inhibitor imatinib have provided important insights into GIST biology. Tumor response is not predicted by KIT expression *per se*, but rather by the presence and type of oncogenic *KIT* mutation.

The most commonly occurring somatic mutations of *KIT* found in GISTs (80–85% of mutations) affect the extracellular and juxtamembrane domains, encoded by *KIT* exons 9 and 11, respectively. In 5–7% of tumors, activating mutations of the homologous *PDGFRA* kinase substitute for *KIT* mutations. Mutant forms of *KIT* (and *PDGFRA*) have constitutive kinase activity that provides a critical tumorigenic stimulus. Tumors that lack *KIT* or *PDGFRA* mutations (10–15%) most likely result from alternative, as yet undescribed, oncogenic mechanisms.¹

Correlation between *in vitro* studies and clinical results with imatinib has been informative. The most common *PDGFRA* mutation (D842V) is not sensitive to imatinib *in vitro*, and tumors with this mutation do not respond to treatment. By contrast, preclinical studies suggested that imatinib would be equally effective against the exon-9-mutant and exon-11-mutant forms of *KIT*, but phase II trials showed poorer responses among the exon-9-mutant tumors,^{2,3} and the current study by Debiec-Rychter *et al.* confirms this finding. The response differences between exon-9-mutant and exon-11-mutant tumors might relate to underlying differences in tumor biology. Whereas tumors with *KIT* exon 11 mutations occur throughout the gastrointestinal tract, those with exon 9 mutations are essentially limited to the intestine, and the subset with *PDGFRA* mutations arises primarily in the stomach. Thus, GISTs may derive from several different (though related) stem-cell populations with varying kinase dependence.

In a randomized, phase III study of imatinib, 400 mg imatinib administered twice daily (high-dose imatinib) yielded superior progression-free survival to the standard dose of 400 mg once daily;⁴ yet, most oncologists prescribe the standard

400 mg daily dose. Side effects are one concern, but these can be reduced through stepwise dose increases. Other concerns include those relating to reimbursement and health authority approval.

Utilizing tumor specimens from the aforementioned phase III study, Debiec-Rychter *et al.* observed that the progression-free survival of GISTs with *KIT* exon 9 mutation is significantly longer at the higher dose of imatinib (400 mg twice daily) than at the lower dose (400 mg once daily). Overall survival was not significantly impacted by dose in any of the genotype groups, including exon 9, but this could reflect high-dose crossovers that were built into the trial and by subsequent treatment with newer agents. Genotype analyses for the US–Canadian phase III trial are in progress. If the results from Debiec-Rychter's group are confirmed, then routine genotyping might be given consideration in dose selection. Early tumor control is desirable, because mutations that confer secondary resistance to imatinib occur in both exon-9-mutant and exon-11-mutant tumors. Genotyping is also relevant to second-line treatment with sunitinib, as tumors with *KIT* exon 9 mutation or a wild-type genotype have superior responses to those with *KIT* exon 11 mutation.⁵ Stratification by genotype will certainly be important in future trials (e.g. frontline imatinib versus sunitinib). Molecular subclassification is becoming an important element in providing personalized care to today's patients with GISTs.

References

- 1 Corless CL *et al.* (2004) Biology of gastrointestinal stromal tumors. *J Clin Oncol* **22**: 3813–3825
- 2 Debiec-Rychter M *et al.* (2004) Use of c-KIT/PDGFR α mutational analysis to predict the clinical response to imatinib in patients with advanced gastrointestinal stromal tumours entered on phase I and II studies of the EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer* **40**: 689–695
- 3 Heinrich MC *et al.* (2003) Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. *J Clin Oncol* **21**: 4342–4349
- 4 Verweij J *et al.* (2004) Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. *Lancet* **364**: 1127–1134
- 5 Heinrich M *et al.* (2006) Sunitinib (SU) response in imatinib-resistant (IM-R) GIST correlates with KIT and PDGFRA mutation status [abstract]. *ASCO Annual Meeting Proceedings*. **24**: 520S–520S

MC Heinrich is a Professor of Medicine at Oregon Health & Science University and Head of Hematology & Medical Oncology at the Portland VA Medical Center, and CL Corless serves as Professor and Vice-Chair of Pathology at the Oregon Health & Science University, Portland, OR, USA.

Acknowledgments

The synopsis was written by Petra Roberts, Associate Editor, Nature Clinical Practice.

Competing interests

The authors have declared associations with the following companies: Novartis and Pfizer. See the article online for full details of the relationship.

Correspondence

*Department of Medicine
Oregon Health & Science
University
R&D-19
3710 SW US Veterans
Hospital Road
Portland
OR 97239
USA
heinrich@ohsu.edu

Received 11 August 2006

Accepted 30 August 2006

www.nature.com/clinicalpractice
doi:10.1038/ncponc0639

PRACTICE POINT

Molecular analysis of GISTs provides useful information for predicting the clinical response to imatinib and may be helpful for individualizing dosage