GIST adjuvant therapy — some answers and more questions

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Imatinib is known to be effective in the first-line treatment of metastatic gastrointestinal stromal tumours. A randomised, placebo-controlled trial has now shown that imatinib is safe and improves recurrence-free survival when used as adjuvant therapy after surgical resection of a primary gastrointestinal stromal tumour.

The current treatment for gastrointestinal stromal tumors (GIST) has become the quintessential example of molecular science translated into practical benefit for patients in a solid tumour model. The finding that inhibition of the critical oncoprotein c-kit, in GIST, has a remarkable effect on tumour cell proliferation has been clinically demonstrated to improve progression-free and overall survival in over 1,700 patients with metastatic disease.[1–3]

Imatinib, a specific small-molecule tyrosine kinase c-kit inhibitor, has proven clinical benefit in over 80% of patients with metastatic GIST, with good oral bioavailability and a low toxic-effect profile. It is now recognised as standard first-line therapy.[1] These data have led to a compelling question regarding the adjuvant use of this agent in the prevention of recurrence of high-risk primary GIST after complete surgical resection (R0).

The American College of Surgeons Oncology Group (ACOSOG) has reported results from the randomised, double-blind, placebo-controlled phase III trial of adjuvant imatinib in patients with primary GIST (Z9001).[4] This trial randomly assigned 713 patients with primary GIST, undergoing either R0 or R1 complete gross tumour resection, to imatinib (n=359, 400 mg/day) or placebo (n=354) for one year as a surgical adjuvant. Patients were eligible for inclusion if they had c-kit positive primary GIST, at least 3 cm in size. The main study endpoint was recurrence-free survival (RFS).

With a median follow-up of 19.7 months, 8% of patients in the imatinib group and 20% of patients

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in the placebo group experienced tumour recurrence or died. The estimated one-year RFS was 98% in the treatment group and 83% in the placebo group. This was a significant benefit in favour of the treatment arm ($P<0.0001$). Overall survival in the two groups was equivalent because of a crossover design, with patients in the placebo group receiving imatinib upon recurrence. Adjuvant imatinib was well tolerated, with the majority of adverse events characterised as grade 1 or 2.

The reported RFS advantage with a 17% absolute benefit for patients in the imatinib group resulted in the FDA – the US regulatory body – giving approval to imatinib as adjuvant therapy in high-risk primary GIST in December 2008. Importantly, this trial provided evidence-based justification for adjuvant therapy that was already becoming accepted clinical practice, even before these results were published. This study will remain a pivotal trial in the management of GIST and will serve as a model for surgical adjuvant trials of targeted therapy in the future. Several European adjuvant trials addressing duration of adjuvant imatinib therapy have been completed and await data maturation, and should add to the accumulating consensus for advising that patients with high-risk GIST be referred to a medical oncologist for a discussion on adjuvant treatment.

However, several important clinical questions remain unanswered. Given that ACOSOG Z9001 did not stratify for mitotic rate, which is an important risk factor in GIST, it is unclear how to integrate this variable into adjuvant indications.[5]

Anatomic location of primary GIST is another important indicator of risk that needs to be evaluated in a trial design. Variable recurrent disease risk assessment suggests that a gastric GIST of >10 cm with a mitotic rate of <5 per 50 high-power field has an expected recurrence risk of 10%.[5] By contrast, the same tumour in the small bowel can have a recurrence risk of >50%.

In ACOSOG Z9001, approximately 40% of patients in each study arm had tumour size >3 cm but <6 cm, and although the study was not powered to assess subsets of patients, RFS was only marginally improved in the comparative treatment or placebo arms of this group. This observation makes the role of tumour size as a criterion for decision making unclear.

In addition, the rate of recurrent disease in the treatment group in this trial seemed to increase significantly, starting at six months after completion of adjuvant imatinib, which certainly suggests that a longer than one year duration of therapy might be beneficial, especially for those patients with a high recurrence risk profile. The current recommendation indicates that adjuvant imatinib be administered for at least a year, but essentially leaves that timeline open-ended.

With regards to overall survival in the ACOSOG Z9001 trial, it is still unclear if there is a long-term survival advantage for those patients initially on imatinib who eventually experience recurrence after completion, compared with those patients in the placebo group with documented recurrence, after both groups are managed with salvage imatinib therapy.

Maturation of these data could address the question of whether the timing of immediate postoperative adjuvant therapy actually provides for a survival advantage.

These questions need to be the subject of future clinical trials and a proposed phase II, five-year, multi-institutional, adjuvant imatinib trial for primary GIST is about to begin accrual. In just a decade we have seen important progress in a disease entity that poses a high risk of recurrence and where metastatic disease was once considered untreatable. However, work still needs to be done.

References

1. CD Blanke et al. (2008) Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. *JCO* 26:620–625

2. C Blanke et al. (2008) Phase III randomized intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. *JCO* 26:626–632

3. J Verweij et al. (2004) Progression-free survival in gastrointestinal stromal tumors with high-dose imatinib: randomised trial. *Lancet* 364:1127–1134

4. RP DeMatteo et al. (2009) Adjuvant imatinib mesylate after resection of localized primary gastrointestinal stromal tumour: a randomized, double-blind, placebo-controlled trial. *Lancet* 373:1097–1104

5. M Miettinen and J Lasota. (2006) Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol* 23:70–83

Practice point

The reported results of ACOSOG Z9001 provide definite evidence of the efficacy of adjuvant imatinib for improvement of recurrence-free survival in high-risk primary GIST.

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