

Recent advances in the management of gastrointestinal stromal tumors

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Abstract

This report focuses mainly on the major reduction of the risk of relapse of gastrointestinal stromal tumor (GIST) treated with imatinib, as identified in the American College of Surgeons Oncology Group (ACOSOG) Z9001 trial. It also focuses on the many unknowns associated with adjuvant imatinib therapy despite approvals by the US Food and Drug Administration and the European Medicines Agency, and on a new marker for the diagnosis of GIST.

Introduction and context

Imatinib mesylate (IM), a small-molecule tyrosine kinase inhibitor, is the standard first-line treatment in advanced gastrointestinal stromal tumor (GIST) disease. Given the high risk of relapse following surgery for localized GISTs, especially for larger tumors, and the efficacy of IM in the advanced setting as well as its favorable safety profile, investigators hypothesized that IM given post-operatively after gross complete resection of primary GISTs could delay or prevent recurrence and therefore improve survival. Thus, three major randomized trials have been investigating the role of a 400-mg daily dose of IM, given for (a) 1 year versus placebo with relapse-free survival (RFS) as the primary endpoint (American College of Surgeons Oncology Group [ACOSOG] Z9001), (b) 2 years versus observation alone with overall survival as the primary endpoint (Intergroup GEIS/EORTC/ISG/FSG/AGITG 62024), or (c) 3 years versus 1 year with RFS as the primary endpoint (Scandinavian Sarcoma Group and the German Association for Medical Oncology [SSG XVIII/AIO] trial). So far, only the ACOSOG Z9001 trial results are available.

Recent advances

The ACOSOG Z9001 study enrolled 713 patients with a localized GIST of greater than 3 cm in diameter [1]. Preliminary data showed a major reduction in the risk of

recurrence, from 17% to 2% at 1 year ($P = 0.0001$), with a hazard ratio of 0.35. In the updated report [2], the difference in RFS was significant for all tumor size subgroups (i.e., 3-6 cm, 6-10 cm, and ≥ 10 cm). Adjuvant IM was well tolerated. No significant impact on overall survival was observed. At the ASCO GI (American Society of Clinical Oncology – Gastrointestinal) meeting in January 2010, Blackstein and colleagues [3] reported all pathologic data (mitotic rate, size, and location of tumor) that were available in 620 patients. The risk of tumor recurrence was estimated using mitotic rate, size, and location according to the classification scheme of Miettinen and Lasota [4]. In the IM and placebo arms, respectively, 2-year RFS rates were 98% versus 98% ($P = 0.92$) for low-risk patients, 98% versus 76% ($P = 0.05$) for moderate-risk patients, and 77% versus 41% ($P < 0.0001$) for high-risk patients. The question of which patient population will most benefit from adjuvant IM is of major importance.

Accurate risk stratification is crucial for the selection of patients who are most likely to benefit from adjuvant IM therapy in clinical practice. Recently, Gold and colleagues [5] developed and validated a nomogram to predict RFS after resection of a localized primary GIST to help guide patient selection for adjuvant IM therapy. The nomogram, which takes into account tumor size (in

centimeters), location, and mitotic index (<5 or ≥ 5 mitoses per 50 high-power fields), has better predictive accuracy, as determined by concordance probabilities, than two commonly used staging systems developed at the US National Institutes of Health GIST workshop in 2001 [6,7]. It has a concordance probability similar to that of the third staging system, the Armed Forces Institute of Pathology (AFIP)-Miettinen system [4]. Nomogram predictions of RFS seem better calibrated than predictions made with the AFIP-Miettinen system.

Very recently, the MetaGIST (Gastrointestinal Stromal Tumor Meta-Analysis Group) [8] published the final data of the two large, randomized, cooperative group studies comparing two doses of IM (400 mg daily versus 400 mg twice daily) in 1640 patients with advanced GISTs and showed that the presence of *KIT* exon 9 mutations was the only significant predictive factor for the benefit of high-dose therapy. They confirmed that among patients with *KIT* exon 9 mutations, progression-free survival (PFS) was significantly longer for patients treated in the high-dose arm ($P = 0.17$).

Recently, Demetri *et al.* [9] reported for the first time a relationship between IM exposure and clinical benefit rates in patients with advanced/metastatic GIST. IM plasma levels showed a high inter-patient variability, and low IM plasma exposure (minimum concentration [C_{min}] <1100 ng/mL) showed a trend of low rate of objective response and a rapid evolution of resistance (short time to progression). These results suggest that a minimal plasma threshold may be necessary to achieve and maintain clinical response in GISTs and that a low C_{min} level of IM (i.e., <1100 ng/mL) might contribute to drug failure in patients with advanced GISTs.

For the treatment of metastatic GISTs that are resistant to both IM and sunitinib, Montemurro *et al.* [10] reported the first results of nilotinib efficacy (400 mg twice a day) in a compassionate use program. The median nilotinib treatment duration was 10 weeks (2 days to 104 weeks), and 21 patients (40%) were treated longer than 12 weeks. Five patients out of 52 (10%, 95% confidence interval [CI] 2-18%) responded to nilotinib, and 19 (37%, 95% CI 24-50%) had disease stabilization. The median PFS was 12 weeks (95% CI 9-15 weeks), and the median overall survival was 34 weeks (95% CI 3-65 weeks). Nilotinib was well tolerated. These findings suggest that nilotinib does have activity in these heavily treated patients, as suggested in the phase I study [11].

Moreover, a major advance was reported in the diagnosis of GIST in 2009. Miettinen *et al.* [12] found that DOG1

(discovered on GIST-1) antibody is as sensitive as c-kit for the diagnosis of GISTs. The authors evaluated this new marker (that was discovered on GIST expression profiles) and c-kit on a large panel of tumors, including GISTs ($n = 1168$) and other tumors ($n = 672$), and normal tissues. The overall sensitivities of DOG1 and c-kit are nearly identical (94.4% and 94.7%, respectively), but DOG1 is slightly better in gastric epithelioid GISTs. Negativity for both markers is observed in 2.6% of GISTs of the gastrointestinal tract. DOG1 is highly specific for GISTs, with a positivity of only 3% in other mesenchymal tumors but a positivity of 20% in gastrointestinal carcinomas.

Agaimy *et al.* [13], like Agaram *et al.* [14] previously, reported that V600E *BRAF* mutations are alternative early molecular events in a subset (4-7%) of *KIT*/*PDGFRA* wild-type GISTs. Agaimy *et al.* [13] demonstrated that the V600E *BRAF* mutation may occur in early-stage incidental GISTs, and are associated with a very low risk of malignant behaviour. These authors reported that mutations in *KIT*, *PDGFRA*, and *BRAF* are mutually exclusive in their study, and like Agaram *et al.* [14], they indicate that *BRAF*-mutated GISTs show a predilection for the small bowel.

Implications for clinical practice

IM has been reported to induce a major reduction of the risk of relapse in the only adjuvant trial for which results are yet available. However, we do not know yet whether adjuvant IM prevents or merely delays relapse, whether it will improve overall survival, or whether specific at-risk populations or molecular subtypes should or should not be offered treatment, and finally we do not yet know the optimal duration of this treatment in these patients. Accurate risk stratification is crucial for the selection of patients who are most likely to benefit from adjuvant IM therapy. The validated nomogram of Gold and colleagues [5] could be used to select these patients. Pathologists should now include DOG1 in the panel of markers for diagnosing GISTs. For patients with metastatic GISTs, the knowledge of the mutational status before starting treatment is useful in choosing the most appropriate dose because patients with *KIT* exon 9 mutations, and only these patients, have a significantly prolonged PFS when they start IM at 800 mg daily.

The results of the nilotinib compassionate program suggest that nilotinib does have activity in these heavily treated patients, but the results of the randomized phase III trial, comparing nilotinib with best treatment according to investigators in GIST patients resistant to both IM and sunitinib, are eagerly awaited.

Abbreviations

ACOSOG, American College of Surgeons Oncology Group; AFIP, Armed Forces Institute of Pathology; AGITG, Australasian Gastrointestinal Trials Group; AIO, Arbeitsgemeinschaft für Internistische Onkologie (German Association for Medical Oncology); CI, confidence interval; Cmin, minimum concentration; DOG1, discovered on gastrointestinal stromal tumor 1; EORTC, European Organisation for Research and Treatment of Cancer; FSG, French Sarcoma Group; GEIS, El Grupo Español de Investigación en Sarcomas (The Spanish Group for Sarcoma Research); GIST, gastrointestinal stromal tumor; IM, imatinib mesylate; ISG, Italian Sarcoma Group; PFS, progression-free survival; RFS, relapse-free survival.

Competing interest

The authors declare that they have no competing interests.

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