Controversies in the Surgical Management of GIST in the Era of Imatinib

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In the pre-imatinib era, surgery was the only effective treatment for gastrointestinal stromal tumor (GIST). However, this treatment modality was often either not possible or insufficient for cure due to the aggressive nature of this disease. The arrival of effective, well-tolerated targeted chemotherapy for GIST mandates new treatment strategies that combine surgery and receptor tyrosine kinase (RTK) inhibitor therapy. The article in this issue by dos Santos Fernandes and colleagues reviews in detail the recent history of GIST treatment, including risk stratification and early clinical trial results. Here, we will summarize key concepts in multidisciplinary management and describe work required to address current knowledge gaps.

Adjuvant and Neoadjuvant Therapy

The standard of care for patients with primary resectable GIST is surgery, aiming for a macroscopically complete resection with negative microscopic margins. The RTK inhibitor imatinib mesylate (Gleevec) was recently approved by the US Food and Drug Administration for use as adjuvant therapy for primary GIST. However, a number of significant clinical issues remain. These include optimal disease risk stratification, length of adjuvant treatment, optimal imatinib dose, and timing of surgery. Each of these will be briefly considered here.

Among patients undergoing macroscopically complete resections with negative (R0 resection) or positive (R1 resection) microscopic margins, 5-year survival rates are as low as 42% to 54%.[1-3] In a 2001 consensus statement released from a workshop convened by the National Cancer Institute, risk of GIST recurrence could be stratified based on primary tumor size and mitotic count.[4] This risk stratification was subsequently revised by Miettinen and Lasota to include tumor site of origin as a key prognostic factor.[5] Tumor rupture and incomplete resection have also been identified as independent risk factors negatively impacting disease-free survival (DFS).[6]

In addition to these prognostic factors, data from clinical trials demonstrated that tumor genotype is an important predictive factor for imatinib response. It is now clear that patients whose tumors contain either Kit exon 9, PDGFR (gene encoding platelet-derived growth factor receptor), or no detectable Kit or PDGFR mutations demonstrate inferior response to imatinib compared to those with Kit exon 11 mutations.[7-10] None of the adjuvant therapy trials discussed below, however, have used a risk stratification model that includes all of these factors. As a result, adjuvant imatinib is generally recommended for patients in all but the lowest risk categories. Future trials should enroll patients based on risk of recurrence according to established risk factors.

Trials of the Use of Adjuvant or Neoadjuvant Imatinib in the Perioperative Management of Gastrointestinal Stromal Tumors
Several trials have explored the role of adjuvant imatinib administered following GIST resection (Table 1). These trials tested durations of adjuvant treatment of 12 months (American College of Surgeons Oncology Group [ACOSOG] Z9000, ACOSOG Z9001, China Cooperative Group), 24 months (European Organisation for the Research and Treatment of Cancer [EORTC] 62024), or 12 vs 36 months (Scandinavian Sarcoma Group [SSG] XVIII). The three 12-month trials have been reported, but are not yet published. Therefore, detailed data including survival rates cannot be shown here.[8,11,12]

The first of these studies to be reported, ACOSOG Z9001, was a phase III trial randomizing patients with completely resected primary GISTs at least 3 cm in size to receive either placebo or imatinib postoperatively for 1 year. This trial was halted early when a planned interim analysis confirmed that recurrence-free survival (RFS) was significantly better in the treatment arm. An important additional observation from this study, however, was that the slopes of the Kaplan-Meier curves representing the two treatment arms were similar. This suggests that adjuvant imatinib delays recurrence but does not increase the surgical cure rate. Thus, the long-term impact of adjuvant imatinib is currently unknown.

This issue will be explored further in EORTC 62024, which, like ACOSOG Z9001, compares placebo to 400 mg imatinib daily, but instead examines overall survival (OS) as its primary endpoint. This study has completed accrual, but no results are available or are expected for quite some time. The SSG XVIII trial, which also recently completed accrual, will in part address the issue of whether 3 years of imatinib results in improved RFS and OS compared to 1 year. However, the eligibility criteria for this trial also allowed enrollment of patients with tumor rupture or metastatic disease, so the data may not be directly applicable to the adjuvant setting. Thus, to date we still do not know the optimal duration of treatment or the long-term benefit of such therapy.

The optimal imatinib dose appears to be related to the mutational status of the primary tumor. The adjuvant trials conducted thus far all tested an imatinib dose of 400 mg daily. For patients with advanced GIST, however, those whose tumors contain exon 9 Kit mutations have improved survival if treated with 800 mg daily. Therefore, another question arising from the reported adjuvant trials is whether the dose of imatinib should be assigned depending on the underlying mutation. A study of this issue would be challenging to conduct, since GIST mutational status is not routinely determined.

**Timing of Surgery and Preoperative Treatment**

TABLE 2

Single-Institution Retrospective Studies of Adjuvant Therapy for Metastatic GIST

Timing of surgery with respect to adjuvant chemotherapy is an important consideration for most solid tumors, and GIST is no exception. Longer-term results from current adjuvant trials should indicate whether adjuvant imatinib improves OS. If it does not, it will be important to know whether administration of adjuvant imatinib is better than waiting until objective disease recurrence. Neoadjuvant imatinib administration was addressed in one multi-institutional trial from the Radiation Therapy Oncology Group, RTOG 0132. This recently published phase II trial treated patients with either resectable primary GIST or resectable recurrent disease with 600 mg per day of imatinib for 8 to 12 weeks prior to planned surgery. Patients who did not progress were eligible for surgery followed by 2 years of adjuvant imatinib at the same dose.[13] Of the patients with primary GIST, 90% demonstrated an objective response prior to surgery, and 92% underwent have not adequately addressed the optimal length and dose of adjuvant and neoadjuvant imatinib therapy, defined the subset of candidates most likely to benefit from such therapy, determined the long-term impact on OS and use of second-line therapy, nor evaluated the extent and timing of surgery in patients with metastatic disease. With the expectation that advances in biology will lead to more effective chemotherapy for a variety of solid tumors, lessons learned in GIST management will provide a model for multimodality treatment that can be broadly applied.

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