EDITORIAL

The Combination of Surgery and Imatinib in GIST: A Reality for Localized Tumors at High Risk, an Open Issue for Metastatic Ones

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Wang et al. update the results of a phase II study on neoadjuvant/adjuvant imatinib mesylate for localized primary and metastatic/recurrent operable gastrointestinal stromal tumors (GIST) with longer follow-up.¹

Although the term *neoadjuvant* correctly applies to a therapy provided in the preoperative setting in patients with primary disease, it is highly misleading when applied to a therapy provided before surgery in patients with metastatic disease. In the former setting, in patients with localized disease, the primary therapy is surgery; imatinib plays an adjuvant/neoadjuvant role. In metastatic disease, imatinib is the primary therapy and should not be discontinued; surgery may play an adjuvant role, although this is not yet proven. Indeed, these two scenarios are quite different. They were separately analyzed and should be separately discussed and put in perspective.

PRIMARY DISEASE

Surgery is the only potentially curative therapy for patients with localized primary GIST. All patients with tumors >2 cm in size should undergo surgical resection.² Imatinib should be provided as an adjuvant treatment in patients with a high risk of recurrence.³ Adjuvant therapy should be administered for at least 3 years on the basis of the results of the SSGXVIII-AIO phase III trial.⁴ This recently reported trial demonstrated improved recurrence-

free survival and, more importantly, overall survival in patients treated with 3 years of postoperative imatinib compared to those treated with 1 year of therapy.

These results expand on the previously published results of the American College of Surgery Oncology Group (ACOSOG) Z9001 phase III trial, which demonstrated that 1 year of adjuvant imatinib improved progression-free survival compared to placebo but failed to demonstrate an overall survival benefit with short follow-up.⁵

In the ACOSOG trial, the benefit applied to patients with tumors carrying sensitive mutations (*KIT* exon 11, *PDGFRA* non-D842V) but did not apply to those with tumors carrying mutations generally unresponsive to lower-dose imatinib (*KIT* exon 9), insensitive to imatinib altogether (*PDGFRA* exon 18 D842V, *KIT* exons 13 and 17, *SDHB*), or with no identifiable mutations at all (so-called wild type).⁶ It is therefore tempting to speculate that the same apply to the survival benefit shown by SSGXVIII-AIO trial.

In the study by Wang et al., the investigators used a dose of 600 mg/day (because the optimal dose had not yet been defined when the trial was launched). It should be emphasized that this is not the current recommended dose for any of the above mutations. Sensitive mutations should be treated with imatinib 400 mg/day.⁷ Increasing the dose does not influence the type or the chance of response. The optimal dose for patients with *KIT* exon 9 mutant primary GISTs is unknown in the adjuvant setting, though in the metastatic setting it is imatinib 800 mg/day.⁸ It is reasonable to consider this dose for patients with localized disease.² Insensitive mutations should not be treated at all.

Critical questions for the surgical oncologist evaluating a patient with a localized, primary GIST are, when should

imatinib be considered in the neoadjuvant setting, and for how long should it be continued? Wang et al. demonstrate that neoadjuvant treatment is feasible, but their study does not truly detail the magnitude of benefit gained by preoperative therapy or delineate the optimal length of therapy.

First, the patient should in principle have a favorable mutational status; otherwise the treatment would be in vain, allowing the tumor to continue growing. Most GISTs will respond, but it should not be forgotten that—especially in gastric location—the amount of insensitive mutations in the localized setting is less uncommon than what has previously been reported.⁹ Although we do not absolutely need to know the mutational status in advance, we should be aware that mutation is an issue. Alternatively, if mutation status is not determined before treatment, we may also check response very early by computed tomography, positron emission tomography, or contrast-enhanced ultrasound.¹⁰ If a radiographic response is detected within a month, then the mutation status is likely favorable, and the treatment may be continued without necessarily pursuing mutation testing. If not, then mutation status should be investigated before continuing the treatment.

Second, the resectability of the tumor and the extent of resection necessary should be considered. Other than presentations of clearly inoperable tumors (which are usually treated with imatinib up front) or symptomatic tumors requiring urgent intervention (hemorrhage, perforation, etc.), there are few reasons today to perform extended procedures (i.e., multivisceral resections or formal organ resections) without first attempting preoperative therapy.¹¹ For instance, patients with large GISTs who may require a

long midline incision for resection may benefit from neoadjuvant imatinib to downstage the operation, potentially converting an open laparotomy approach to a laparoscopic one. Figure 1 illustrates a patient with a large primary gastric GIST measuring 16 cm at presentation. After 6 months of neoadjuvant imatinib, the tumor measured 10 cm and could be resected via a laparoscopic partial gastrectomy. Another typical circumstance in which neoadjuvant therapy may be beneficial is in patients with GISTs arising in the esophagus, gastroesophageal junction, duodenum, or distal rectum. Preoperative treatment may shrink the tumor and allow a more conservative local excision. Figure 2 provides the example of a distal rectal GIST that, after neoadjuvant therapy, could be resected with a perineal excision instead of a formal rectal resection. A transanal approach could have also been an alternative. In general, such patients would normally also undergo postoperative adjuvant treatment because of the expected recurrence risk.

The chance of obtaining a response is high and the benefit for tumor shrinkage obvious, so this approach should always be discussed for patients affected by bulky and/or poorly located disease (esophagus, gastroesophageal junction, duodenum, distal rectum), as well as for those who would be candidates for an adjuvant treatment anyway.

Third, in the study of Wang et al., patients underwent surgery between the second and third month. It is now well known that the preoperative treatment may result in sustained tumor shrinkage if provided for a longer duration.¹² Surgical resection may then be performed between the 6th

- Laparoscopic partial gastrectomy

FIG. 1 Contrast-enhanced computed tomographic scan of primary gastric gastrointestinal stromal tumor before (right) and after (left) preoperative imatinib for 6 months. Macroscopic appearance of tumor remnant at laparoscopy, before resection

- Local excision through perineal approach

FIG. 2 Contrast-enhanced magnetic resonance image of primary low rectal gastrointestinal stromal tumor before (*right*) and after (*left*) preoperative imatinib for 8 months. Because the tumor harbored an

exon 9 mutation, the patient was treated with a higher dose. Surgery consisted of local excision rather than a formal low anterior resection

and the 12th month, or sooner if the treatment effect plateaus. This allows for optimal tumor shrinkage, or at least shrinkage to the point where there is no further benefit to be gained by further neoadjuvant therapy without the risk of developing secondary resistance.^{11,12} As previously already observed, imatinib can be safely stopped the day before surgery and restarted as soon as postoperative normal feeding is restored.^{13–19}

After surgery, patients in the study were allowed to continue therapy for 2 years. The recommendation based on the most current data would be to continue therapy for a total of 3 years. It is not clear, however, whether the 3 years of therapy should be entirely postoperative, or whether it may include the neoadjuvant course. Determining a patient's risk of recurrence after undergoing preoperative therapy is challenging because the mitotic count of the surgical specimen is no longer accurate nor representative of the pretreatment mitotic count. Nevertheless, it is very unlikely that a patient for whom preoperative treatment is considered had a low-risk tumor. Therefore, once we initiate treatment in the preoperative setting, we are committing to treat that patient with imatinib for an additional 3 years.

METASTATIC DISEASE

Imatinib is the standard first-line treatment for metastatic GIST. The dose—as above—is 400 mg/day except

for patients affected by tumors harboring a *KIT* exon 9 mutation, where 800 mg/day is indicated.⁷

Patients affected by metastatic GIST in the study of Wang et al. were initially scheduled to stop treatment 2 years after surgery. This cannot be recommended today outside of a clinical trial because it is well documented how quickly and inevitably recurrence occurs after imatinib withdrawal in patients with metastatic GIST, even if completely resected.²⁰ The investigators in this study appropriately amended the trial to continue indefinite treatment in the recurrent/metastatic cohort. Imatinib is a chronic therapy and should not be interrupted unless unacceptable toxicity and/or disease progression are documented.

The question remains whether to consider surgery in patients whose disease responds to imatinib to potentially prolong its activity. No data are available so far to support this indication. The present study does not really contribute to our understand of this issue. Two trials addressing this question were started in Europe (<http://clinicaltrials.gov/show/NCT00956072>) and in China (<http://apps.who.int/trialsearch/trial.aspx?trialid=ChiCTR-TRC-00000244>), but both failed to recruit fast enough to meet the target accrual (12 patients were recruited in the European trial and 41 in the Chinese one). This thus remains an open question.

Several single-institutional series consistently reported how feasible and safe it is to operate on these patients.^{13–19}

Similar results were obtained in patients treated by Wang et al.

The only way to obtain more reliable data on the possible effect of “adjuvant” cytoreductive surgery for patients in response to imatinib is by a prospective observational study. The nonrandomized evidence thus generated would be prospective, contrary to the retrospective nature of published case series analyses on cytoreductive surgery for residual disease in advanced GIST undergoing imatinib treatment and demonstrating ongoing disease stability or response. Of course, there would be a selection bias in the absence of a randomized treatment assignment. Thus, an effort should be made to consider all sources of biases in the study design, and in the analysis and interpretation of results. At each participating center, eligible patients, after being properly informed, could be offered the choice between the two treatment options: surgery plus maintenance therapy with imatinib, or maintenance therapy with imatinib alone. The relative efficacy of the two treatment strategies would be evaluated first by comparing the outcome of patients who chose to undergo surgery versus those who did not (*primary analysis*), and second by comparing the outcome in centers where the proportion of patients choosing surgery was high (i.e., greater than the overall proportion in all centers combined) versus the outcome in centers where this proportion was low (*explanatory analysis*).

An effort to build such a study is presently under way and will, we hope, provide data on which to base our future decisions.

A separate question is what to do once limited progression to imatinib is detected. Many experienced centers will consider and offer cytoreductive surgery as salvage therapy in an effort to prolong the time the patient can continue to receive imatinib and postpone the switch to a second-line treatment. Such decisions should be made on a case-by-case basis.^{2,3}

CONCLUSIONS

For patients with localized disease, preoperative treatment with imatinib should always be considered when the expected recurrence risk is not low, the location is difficult, surgery is expected to involve an entire organ or multiple organs, or a more conservative approach could be achieved. Knowing mutational status would be ideal, but alternatively tumor response may be evaluated. After the operation, imatinib should be continued in the adjuvant setting for at least 3 years.

For patients with metastatic disease, imatinib is the standard treatment, with the only limiting factor being the occurrence of secondary resistance. To date, no data are

available to confirm a possible adjuvant role for cytoreductive surgery to prolong imatinib activity, though further study is necessary; at present, such extensive surgery may be performed at centers with extensive experience. Salvage surgery could be considered once imatinib starts failing to a limited degree.

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