Cytoreductive Surgery in Advanced GIST: Timing is Everything

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The success of imatinib mesylate in the treatment of metastatic gastrointestinal stromal tumor (GIST) has revolutionized the multidisciplinary management of this disease. The resounding benefit of this drug in improving survival has been further extended by second- and third-line tyrosine kinase inhibitors (TKIs) sunitinib malate and regorafenib, respectively. However, the utility of each drug has been limited by the almost inexorable development of drug resistance in most patients who receive each drug. Therefore, an implicit goal of therapy is to maximize the benefit of each drug by expanding its therapeutic window as much as possible and delaying institution of the next-line therapy.

Optimal timing of drug therapy is one way of doing so. The European Organisation for Research and Treatment of Cancer 62024 trial evaluated timing of imatinib therapy in patients with primary GIST to determine if adjuvant imatinib administered for 2 years after resection of primary GIST improved imatinib failure-free survival. This study, recently reported at the American Society of Clinical Oncology, confirmed data from previous studies that adjuvant imatinib improved recurrence-free survival.^{1,2} However, it did not improve time to institution of next-line therapy after imatinib failure, the primary end point.³

Another potential way to delay institution of next-line therapy is to add cytoreductive surgery as an adjuvant treatment to standard-of-care TKI therapy in patients with metastatic disease. We do not know whether surgery really adds any benefit at all in terms of progression-free,

recurrence-free, or overall survival (PFS, RFS, or OS). Attempts to answer this question in randomized trials have failed as a result of poor accrual. We do know, on the basis of retrospective data, that patients with response to TKI therapy at the time of surgery have better outcomes than those with multifocal progression at the time of surgery.^{4–6} We do not know whether cytoreductive surgery performed up front for metastatic disease, before institution of imatinib therapy, carries any benefit at all.

In their article in this issue, An et al. have addressed this last unknown issue.⁷ It is a clinically relevant question that we as surgical oncologists face—not only in GIST but in other malignancies as well: when metastatic disease amenable to surgery is first diagnosed, should we operate or offer systemic therapy as the initial line of therapy? The authors performed a single-institution, retrospective analysis evaluating the impact of initial cytoreductive surgery (debulking $\geq 75\%$) followed by imatinib to initial imatinib (with or without subsequent surgery and/or radiofrequency ablation) in patients with metastatic GIST.

Not surprisingly, patients undergoing initial surgery were generally better candidates for surgery (younger age, better performance status), with metastatic disease presenting initially rather than as a recurrence and with more peritoneal rather than liver disease. Tumor volume, importantly, was similar in the two cohorts. Even with the favorable bias for the initial surgery cohort inherent in such a retrospective study, initial surgery did not improve PFS or OS. Furthermore, up-front cytoreductive surgery also did not alter the frequency of subsequent salvage therapy compared to the control cohort. One could infer that if patients in the two cohorts were similarly matched not only for tumor volume but also for age and performance status, it is conceivable that those with initial TKI therapy may have done better; a matched cohort analysis may be able to answer this.

The potential advantages for upfront surgery seem obvious: by debulking tumor volume, the patient starts subsequent systemic TKI therapy with overall less tumor bulk. It is well established that larger tumor volume correlates with worse outcome in patients with metastatic GIST.^{8,9} This was again confirmed in this study as well, but only when examining initial tumor volume at presentation, not tumor volume at the start of TKI therapy. The authors found that large tumor size at presentation correlated with worse PFS and OS on multivariate analysis.

It is possible that if the authors had classified only patients with a macroscopically complete resection as having cytoreductive surgery, a statistically significant difference in PFS or OS could have been apparent, but it is possible that this would have reduced the numbers sufficiently to preclude a useful analysis.

Such an issue of the timing of the operation is not unique to this disease by any means. It has been argued extensively for even primary, nonmetastatic neoplasms. For instance, for years, the use of neoadjuvant therapy for primary pancreatic cancer has been debated. One of several points made in favor of neoadjuvant therapy before surgery is that patients whose disease progresses or who develop radiographic evidence of metastatic disease during neoadjuvant therapy are spared an operation from which they would derive little, if any, benefit. This is based on the presumption that these patients had occult metastatic disease at diagnosis, and thus surgery would not be curative or beneficial. The same argument could be made here. By starting TKI therapy first, only patients with metastatic GIST whose disease responds to therapy and who do not experience disease progression in a multifocal manner may derive some benefit relative to the others. Timing is critical, and biology trumps all.

The only way to really answer this question is through a phase III design, but the failure of the other phase III GIST metastasectomy trials has certainly soured enthusiasm for answering this question in a randomized study.

The authors tackled a tough question. Elective, non-emergent initial cytoreduction likely has no beneficial role in patients with metastatic GIST and is best avoided. The inherent biology of the tumor essentially trumps all. Tumor volume at presentation is predictive of outcome, not tumor volume at start of systemic therapy. Metastatic GIST is

rarely curable, so cytoreductive surgery, when considered, should be reserved as an adjuvant therapy for patients whose tumor biology, as evidenced by response to TKI therapy, is favorable, or it may be presented as a salvage therapy for patients who experience limited disease progression after response in order to delay as much as possible switching to the next line of therapy.

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