Editorial Commentary

The past, present, and future: the evolving role and challenges of surgery in the multimodal management of gastrointestinal stromal tumors

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The tyrosine kinase inhibitor (TKI) revolution for the treatment of gastrointestinal stromal tumors (GISTs) is one of the major success stories in cancer medicine and for targeted therapy. Prior to the advent of TKI treatment, GIST management was limited to multiple surgical debulkings and ineffective chemotherapy (1,2). First evaluated in 1998 in a phase I clinical trial to treat chronic myeloid leukemia (3), imatinib showed activity against multiple tyrosine kinase targets with modest adverse effects. Shortly thereafter, imatinib was tested in a 50-year-old Finnish woman who had previously undergone multiple cytoreductive surgeries for metastatic GIST, including a proximal gastrectomy, omentectomy, oophorectomy, partial colectomy, partial hepatectomy and removal of 45 other small metastases (4). Confirmatory genetic testing showed a c-kit mutation in exon 11 and a month after initiation of therapy, she showed a complete metabolic response. This then led to the first formal phase I study conducted by the European Organization for Research and Treatment of Cancer (EORTC) (5) and eventual widespread adoption of imatinib.

Surgery in the post-imatinib era also changed dramatically with fewer radical surgeries, more organ-preservation and lower rates of local recurrence (6,7). In their review, Yonkus *et al.* highighted the various iterations of TKIs that have been developed and the role of targeted therapy in the perioperative setting (8). Despite the tremendous impact TKIs have had on survival in patients with advanced and metastatic GISTs, secondary resistance is common and complete elimination of the disease is rare (9,10). Resistance to therapy may be caused by tumor cells that evade treatment induced apoptosis and enter quiescence with a resurgence when imatinib is held or cell cycle mechanisms adapt. This highlights the need for more clinical trials and rigorous studies on newer TKIs such as ripretinib and avapritinib that can potentiate or obviate the well-known benefits of imatinib.

The role for surgery for advanced GIST patients has also evolved with the increased use of TKIs. When patients have good response on imatinib, the benefits of cytoreductive surgery must be weighed heavily against surgical morbidity. Surgery can now be utilized as a consolidative treatment to resect residual disease in patients who achieve good response to TKI therapy or as an adjunct in patients with either stable disease or mixed response with limited sites of progressive disease on therapy. As Yonkus *et al.* pointed out, cytoreductive surgery in combination with imatinib in which R0 and R1 resections is achieved will likely lead to improved oncologic outcomes. That data are mixed in patients who have moved on to second- and third-line therapies after progression on initial treatment. Yonkus *et al.* discussed the two conflicting studies by Raut

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and Yeh on the benefit of cytoreductive surgery for GIST in patients on sunitinib treatment (11,12). However, these studies examined two different populations of patients; 80% of patients in the Raut *et al.* study had some form of disease progression at time of surgery (11) while in the Yeh *et al.* study 23% of patients had progressive disease and 7.7% had stable disease. These differing study populations demonstrate that the tumor response to sunitinib is mostly like the major driver of oncologic outcomes over surgical debulking and one must tailor their surgical management based on the disease biology. We agree that categorization of responsiveness to TKIs in those with metastatic GIST should be a major factor when assessing for surgical eligibility as those who are not responsive to TKIs will likely not derive major benefit from surgery. In those who have moved on to second- and third-line TKIs, responsiveness to their current TKI remains paramount to their long-term oncologic outcomes but given their history of failure on TKI, the benefit in those patients is likely to be less pronounced than in those on first-line therapy. Thus, the optimal role of surgery in patients who have failed first-line TKI therapy remains a clinical challenge.

GIST management is appropriately becoming increasingly individualized based on mutational profiling. Mutational profiling is a valuable tool to help predict response to therapy and guide selection of suitable TKIs, particularly with the advent of the newest generation of TKIs. Unfortunately, this tool is often underutilized with a large portion of patients not undergoing appropriate exon mutational analysis (13). As our knowledge improves regarding the impact of specific exon mutations, we need to incorporate this information into our surgical decision-making process. Shen *et al.* reported KIT exon 11 deletions involving two or more codons, homozygous exon 11 mutations and intron 10/exon 11 junction deletions portend high recurrence rates and poor prognosis (14). Additional studies have shown other specific exon 11 mutations indicate more aggressive tumor biology (15) and high recurrence rates. Incorporation of findings beyond basic exon mutational information is warranted for stratification of this heterogenous group of tumors. For patients being considered for cytoreductive surgery, particularly in cases where morbid surgery is being considered, high-risk mutational profiles should be factored into decision-making process. Beyond mutational analysis, significant advances have been made in gene expression profiling which may be the next frontier in identification of high-risk tumors. Gene expression profiles have already been linked to response to TKIs (16) and may potentially correlate with the benefit of cytoreductive surgery. Nowak *et al.* analyzed 56 GIST cases using a 231 gene expression panel (17). Using the results from the 56 cases, they identified a 7 gene set which performed well in prognostication. Tools utilizing gene expression profiling may add useful complementary information when faced with difficult clinical scenarios.

As we begin to understand the molecular and genetic underpinnings of GIST tumors in greater detail, our ability to accurately predict response to therapy and determine patient prognosis will continue to improve. In parallel with these advances, we need to incorporate objective measures of tumor biology to determine resectability as well as the potential overall oncologic benefit versus the risk of surgery in patients with advanced GIST. While TKIs have improved survival, their ability to achieve durable long-lasting tumor control and/or eradication remains limited and nuanced decisions regarding surgery in the contemporary clinical context of having multi-generations of available TKI therapies remain challenging but essential. The addition of objective measures such as mutational and gene expression profiles will help guide appropriate management.

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