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Also in This Issue: Surgical Management and Clinical Outcomes in Rare GIST

New Targets, Novel Treatments Suggest Future Strategies

An Educational Service for Medical Oncologists, Gastroenterologists and other GIST Care Providers

Editorial Mission
The GIST Cancer Journal is intended to serve as a comprehensive and authoritative resource of scientifically valid information for physicians and allied health care professionals regarding advances in the diagnosis and treatment of gastrointestinal stromal tumors. Editorial content focuses on the impact of translational research in oncology and gastroenterology relating specifically to GIST. As the official medical journal of the Life Raft Group, it also provides a forum for GIST patient advocacy. *The GIST Cancer Journal* is circulated to all medical oncologists and other selected medical professionals, and is available to members of the GIST community upon request

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About the cover
A broader spectrum of targets is taking shape and downstream mechanisms only recently recognized are part of new strategies investigated at the bench. Photo indicates new molecules in development for GIST. Copyright © iStock/Getty Images.

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Editor's Memo

Drugs in the Pipeline for GIST: Have We Reached a Turning Point?

Drug development for cancer has benefited from both new FDA policies and advances in genetic analysis that allow researchers to target drugs to patients most likely to benefit. Between 2010 and 2014, the FDA approved 37 oncology drugs, compared to just 19 between 2005 and 2009. This year it has approved four more, according to a Bloomberg Business report.

Although the FDA's speedier approval process is encouraging news for drugs in the pipeline for gastrointestinal stromal tumors (GISTs), I am even more encouraged by the research into innovative strategies and avenues for treating the disease. All of the new approaches highlighted in this issue by Anette Duensing, MD, raise a tantalizing question: Have we reached a "turning point" in the management of this disease that enables us to broaden the spectrum of therapy and get beyond the traditional avenue of tyrosine kinase inhibition? Use of the term "turning point" is deceptive per se and somewhat illusory. A true turning point might be the approval of a new drug by the FDA for GIST. On the other hand, it might be defined as results so promising the drug has entered Phase 3 trials or even been given "fast track" status by the FDA. Drug development and approval is a continuum and it only occurs in incremental steps. Thus, I tend to take a dim view when I hear of "breakthroughs in therapy" or a new "milestone."

Some of the molecules at various stages of study have not reached the so-called "turning point" everyone is looking for. But perhaps and within a few years, the list of new drugs approved by the FDA might include some of the novel therapies mentioned in Dr Duensing's exciting report, the first segment of a two-part series in the journal on drugs in the pipeline. In the second part, she will provide an update on the trials themselves and the progress to date in evaluating new compounds as the protocols approach or have achieved full enrollment.

These trials and future studies will need to pursue several directions emerging from recent findings. Because most imatinib-resistant GISTs develop secondary mutations within the KIT or PDGFRA kinase domains, novel therapeutic approaches that do not directly target these kinases are particularly important.There are some intriguing questions raised by these new investigations, including the surprising revelation that chemotherapy may have a role in GIST treatment.

- Could some GIST cells, for example, have an unexpectedly high and specific sensitivity to certain types of FDA-approved chemotherapeutic agents?
- How could compound screening of these agents identify unexpected drug sensitivities?

(continued on next page)

The GIST Cancer Journal Author Guidelines

Scope of Manuscripts
The GIST Cancer Journal considers the following types of manuscripts for publication:

- Reviews that summarize and synthesize peer-reviewed literature to date on relevant topics in a scholarly fashion and format.
- Original contributions based on original, basic, clinical, translational, epidemiological, or prevention studies relating to gastrointestinal stromal cancer that are well documented, novel, and significant.
- Letters to the Editor on timely and relevant subjects pertaining to the diagnosis and treatment of gastrointestinal stromal tumor.
- Clinical case studies.

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Length: Full-length manuscripts should not exceed 4000 words, including references. Please limit the reference list to 50 citations. Manuscripts should be accompanied by figures and/or tables. Generally 4-5 figures and 2-3 tables are preferred for each manuscript. Please include a brief description to accompany these items, as well as a legend for all abbreviations. Manuscripts should not contain an abstract but an introduction is recommended.

Spacing: One space after periods. Manuscripts should be double spaced.

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All submissions should have references that are referred to in the text by superscripted numbers and that conform to AMA style.

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Editor's Memo *(continued from page 2)*

- What inhibitory processes, heretofore unknown, could enhance imatinib-induced apoptosis, thereby overcoming the quiescence observed in GIST cells treated with imatinib?

As agents such as bortezomib (Velcade) undergo additional study in GIST, a further question concerns to what extent they might be combined with imatinib or perhaps used to greater effect if administered in sequence. The underlying excitement, however, relates to the identification of new targets, some downstream, previously unrecognized. Who knew, for example, a few years ago, that something mysteriously called the DREAM complex plays a role in GIST biology? New insights are beginning to elucidate other process within the GIST "machinery." For example, imatinib-treated GIST cells develop massive upregulation of a protein of the H2A family, histome H2AX. A recent report demonstrated that H2AX was a potent inducer of apoptosis in GIST cells. The key finding in this work was that H2AX was regulated by the ubiquitin-proteasome machinery in GIST cells and that proteasome inhibition is an important strategy. With the addition of these new concepts, our lexicon is changing as well. Hopefully, these changes will lead to a broader spectrum of treatment and greater options for managing GIST.

Jonathan C. Trent, MD, PhD
Editor-in-Chief

New Targets, Novel Treatments Could Achieve Translational Results and Enhanced Apoptosis of GIST Cells

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The landscape of GIST treatment is changing rapidly as is much of the rationale for using traditional approaches. A broader spectrum of targets is taking shape and downstream mechanisms only recently recognized are part of new perspectives as recent reports explore efforts to downregulate KIT and other pathways. It is time to reconsider and reassess traditional concepts of imatinib resistance and sensitivity and view the disease through insights beginning to emerge.

New windows of opportunity are beginning to open for the treatment of gastrointestinal stromal tumors (GIST), novel strategies based on innovative concepts are emerging, and a remarkably different view of the biologic alterations of the tumor could usher in improved approaches to management.

These exciting developments have also prompted a reevaluation of treatment options, such as chemotherapy, that could bring clinicians closer to the elusive goal of a personalized approach, even for patients with GIST resistance to tyrosine kinase inhibitors (TKI). On the other hand, it could presage a reassessment of how TKIs, notably imatinib, might be used in combination with novel agents to overcome the resistance to TKI therapy. Progress in these new investigative areas has been moving along at a swift pace, and while it is still too early for new findings to have a translational impact on clinical practice, the implications for significant changes in our approach to GIST are apparent.

Most GISTs are caused by activating mutations of the *KIT* or *PDGFRA* (platelet-derived growth factor receptor alpha) receptor tyrosine kinase genes.[1-4] Imatinib treatment remains the cornerstone of therapy, but complete remissions are rare and up to 50% of patients with GIST develop resistance during the course of the first 2 years of systemic treatment.[5] Novel therapeutic options are needed to produce disease stabilization, achieve symptomatic benefit and delay the occurrence of resistance mainly caused by secondary mutations of the driver oncogenic kinase.[6,7] Much of the focus emerging within the last two years has been on agents that do not involve kinase inhibitors, but until recently

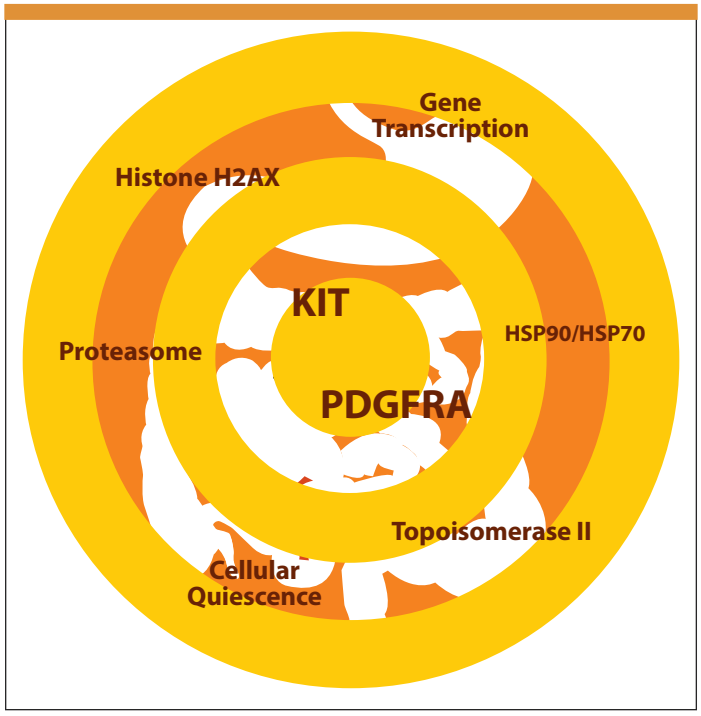

Figure 1. Conceptual illustration suggests new approaches in targeted therapy. At center are KIT and PDGFRA, traditional targets, but on the periphery are new areas of exploration.

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Key words: GIST, novel treatments, bortezomib, DREAM complex, chemotherapy, KIT, PDGFRA

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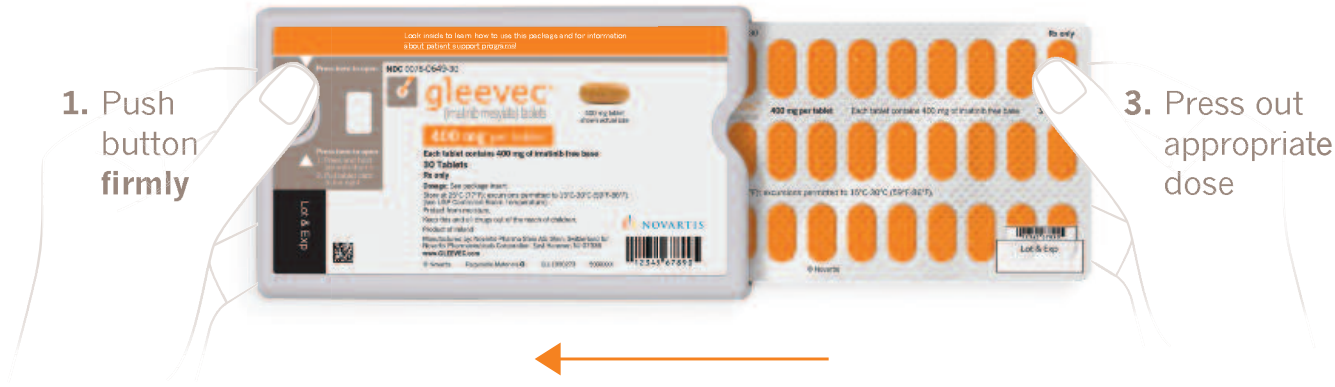

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these avenues have remained largely unexplored.

This is why a new generation of studies is of importance, not only for their potential advantages in resolving the riddle of TKI resistance but in how they can reveal more about the biology of the disease itself and what targets may help to optimize treatment (**Figure 1**). These new studies raise many questions about how approaches can be modified and what targets can be addressed. The development of alternative approaches to treat patients with GIST who have failed first and second line therapies is imperative.[8]

- What are the exact mechanisms of action of imatinib with respect to inducing apoptosis (programmed cell death)? And is it possible to target these pathways, potentially using existing drugs that are already FDA-approved?
- Could compound screening strategies identify unexpected drug sensitivities, e.g. of certain types of FDA-approved chemotherapeutic agents?
- What happens to GIST cells that do not die after imatinib treatment? Clinical observations suggest that they are entering a state of cellular quiescence ("cell sleep"). If successful cancer therapy is hindered by tumor cell quiescence because these cells remain viable and a reservoir for tumor progression, what are the latest advances to address the key regulators involved in this process?
- What inhibitory processes could overcoming the quiescence observed in GIST cells treated with imatinib thereby enhancing imatinib-induced apoptosis?

Histone H2AX, Mediator of Imatinib-induced Apoptosis

New studies have begun to elucidate the process of GIST cell apoptosis following imatinib treatment. Here, one observation emerged as puzzling: kinase inhibition was a rapid effect that occurred within minutes; however apoptosis took considerably longer — approximately 3 days. There seemed to be no explanation for what occurred during the lag period between kinase shutdown and apoptosis.

In a recent study, we could show that imatinib-treated GIST cells developed a massive upregulation of a member of the nuclear core histone proteins, histone H2AX.[9] We demonstrated not only that H2AX was a potent inducer of apoptosis in GIST cells, but also that the upregulation of H2AX occurred during the aforementioned lag period. Further findings reported in the study indeed suggest that histone H2AX is causatively involved in imatinib-induced apoptosis. Experimentally reducing H2AX levels in GIST cells protects them from imatinib-induced cell death, while overexpressing H2AX kills the cells. Moreover, histone H2AX levels are still increased after imatinib, even when downstream mechanisms of apoptosis are blocked with a chemical inhibitor. These findings indicate that H2AX upregulation is a direct consequence of imatinib treatment and that upregulation of histone H2AX could be targeted therapeutically in GIST.

Here, another key finding of our study came into play. While examining the mechanism of action of histone H2AX turnover, we discovered that H2AX protein levels are regulated by the ubiquitin-proteasome machinery in GIST cells. Moreover, experimental inhibition of the proteasome led to increased levels of H2AX. This led to an important follow-up study,[10] in which we asked whether it would be possible to trigger GIST cell apoptosis with the proteasome inhibitor bortezomib (Velcade), an agent previously FDA-approved for multiple myeloma.[10]

Proapoptotic Activity of Bortezomib: Downregulating KIT, Inhibiting the Proteasome

Indeed, when we tested the activity of bortezomib in GIST cells (at equal concentrations as had been used against multiple myeloma), evidence for the proapoptotic activity of the drug in GIST was shown.[10] We could demonstrate that bortezomib caused cell death not only in imatinib-sensitive GIST cells, but also in imatinib-resistant GIST cells and a short-term culture derived from an imatinib-resistant GIST. Thus, it can be feasible to induce apoptosis in GIST despite the presence of resistance mutations as long as proper mechanisms are targeted.

However, two intriguing findings, one expected and the other not anticipated, were discovered when studying the mechanism of action of bortezomib in GIST.

1. As hypothesized, bortezomib-treated cells showed a significant increase in the levels of soluble H2AX.
2. Bortezomib-treated cells showed an almost complete loss of the KIT kinase protein itself (**Figure 2**).

Thus, it appears that bortezomib has a dual negative effect on GIST cell viability – upregulation of the pro-apoptotic histone H2AX and downregulation of the oncogenic KIT kinase.

These findings raise the question about how bortezomib can induce such a dramatic loss of KIT protein expression. Intuitively, it would appear that inhibition of the proteasome and hence inhibition of proper proteolytic turnover leads to an accumulation of proteins in the cell. Unexpectedly, we could demonstrate that bortezomib causes a transcriptional downregulation of *KIT* resulting in a profound loss of KIT protein expression. Although this activity appears to be associated with an inhibition of the global transcriptional machinery, GIST cells are especially sensitive to the loss of ongoing *KIT* transcription and expression. Moreover, previous work has shown that mutant KIT protein is less stable compared to wild type protein.[11] It is therefore highly likely that constant KIT protein production is necessary to provide ongoing oncogenic stimulation. Together, these results imply that GISTs are prone to transcriptional inhibition, a concept also suggested by other authors.[12] Therefore, using transcriptional inhibitors could be a novel therapeutic strategy to induce GIST cell death.

Furthermore, additional mechanisms could be involved in the downregulation of KIT protein expression and induction of apoptosis by bortezomib. For example, bortezomib has been implicated of being involved in the regulation of chaperone proteins, such as HSP90 and HSP70.

Future studies will need to pursue several directions emerging from these findings. Because most imatinib-resistant GISTs develop secondary mutations within the *KIT* or

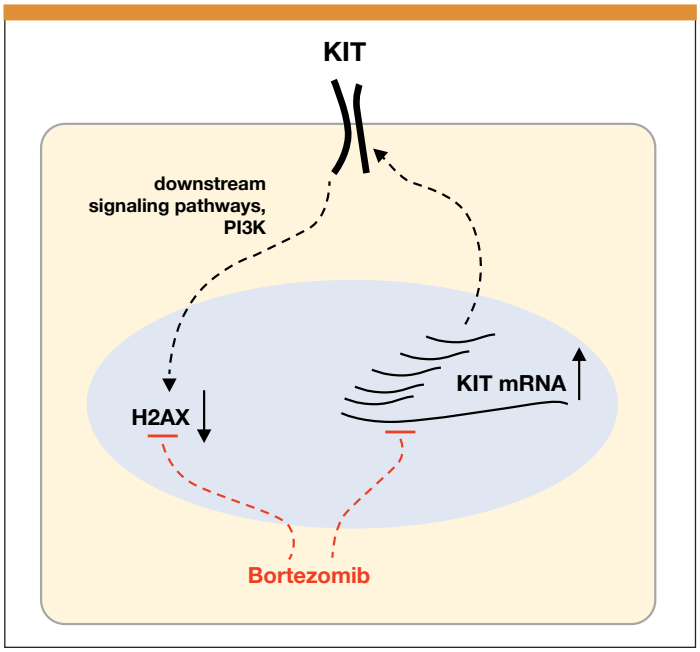

Figure 2. Bortezomib reverses two aspects of GIST cell biology. GIST cells rely on a high rate of ongoing KIT transcription in order to maintain continuous expression of the less stable mutant protein and hence oncogenic signaling. Previous results have shown that one function of oncogenic KIT is to downregulate expression of the pro-apoptotic histone H2A family member H2AX through protein degradation. Treatment of GIST cells with bortezomib was found to increase H2AX levels, which can lead to soluble non-nucleosomal H2AX and enhanced cell death. At the same time, bortezomib was found to trigger an almost complete loss of KIT protein expression involving a transcriptional shut-down. Soluble H2AX itself can block ongoing gene transcription, so it is possible that this activity contributes to the downregulation of KIT transcription in bortezomib-treated cells. It is also possible that downregulation of other mRNAs than KIT plays a role in this process since a general inhibition of RNA polymerase II-mediated gene transcription was observed. Note: The precise intracellular site and mechanism of H2AX proteasomal degradation remains to be determined. Adapted from Ref 8.

PDGFRA kinase domains, novel therapeutic approaches that do not directly target these kinases, such as bortezomib, are particularly important.[10] Detailed animal studies corroborating this concept are still needed, however, preliminary results indicate that bortezomib does have activity *in vivo*.[10,13] The promising message to emerge from our report is that bortezomib is effective against GIST cells harboring various resistance mutations, including the so-called gatekeeper mutation. Therefore, the activity of bortezomib in GIST cells suggests that its apparent dual mode of action – stabilization of histone H2AX and transcriptional downregulation of KIT – needs to be evaluated in clinical trials involving GIST patients.

Chemotherapy for GIST? Compound Screening Yields Surprising Results

As detailed above, treatment strategies that do not focus on kinase inhibitors could lead to additional options in therapy. One of the latest lines of investigation has turned toward a reassessment of GISTs to chemotherapy. Although it is commonly believed that GISTs respond poorly to chemotherapeutic agents, this notion is rooted in earlier clinical trials. These earlier trials were completed before *KIT*/*PDGFRA* driver mutations in GIST were identified and before diagnostic markers, such as immunohistochemistry for KIT, enabled a reliable diagnosis of GIST. Hence, these earlier clinical trials included patients with gastrointestinal leimyosarcoma, a tumor highly resistant to chemotherapy.

Behind this background, our group performed a compound screen of FDA-approved chemotherapeutic agents (NCI Approved Oncology Drugs Set II) in GIST cell lines.[14] Although the study confirmed that GIST cells were resistant to most chemotherapeutic agents, GIST cells displayed an unexpectedly high sensitivity to transcriptional inhibitors and topoisomerase II inhibitors.

Several findings were among the highlights of this study:

1. These compounds were active in imatinib-resistant GIST cells, including patient-derived, primary tumor cells.
2. Minimal effective concentrations defined in this study are clinically achievable in humans.
3. Two compounds that were tested in further detail (mithramycin A, an indirect inhibitor of the SP1 transcription factor, and mitoxantrone, a topoisomerase II inhibitor) exerted significant antitumor effects in mouse xenograft models of human GIST.
4. The mechanism of action of the above-mentioned drugs exploits the dependency on continuous KIT expression and/or intrinsic DNA damage response defects in GIST cells.

Mithramycin A has previously been shown to bind to GC-rich promoter regions, thereby replacing the transcription factor SP1 from DNA.[15,16] Through this mechanism, the agent inhibits the transcription of SP1-regulated genes. Intriguingly, SP1 is a major transcriptional activator of the *KIT* gene.[17] Its inhibition in GIST cells by mithramycin A thus led to a substantial decrease of *KIT* mRNA and protein expression and hence reduced KIT activation. This finding most likely explains the apoptotic effect of mithramycin A on GIST cells.

The study also addressed why topoisomerase II inhibitors, such as mitoxantrone, may be effective in GIST (**Figure 3**). These agents are known to induce DNA double strand breaks by inhibiting the DNA unwinding activity of the enzyme topoisomerase II. This was confirmed in GIST cells *in vitro* by showing a rapid activation of the ATM kinase as well as the induction of DNA breaks. The effectiveness of mitoxantrone in GIST cells was likely linked to their specific expression levels of the topoisomerase I and II enzymes.

Although the transcriptional inhibitor mithramycin A and the topoisomerase II inhibitor mitoxantrone were effective as single drugs in imatinib-sensitive and imatinib-resistant GIST cells, our study raises the possibility that combinations of imatinib could enhance their antineoplastic effect. While preliminary experiments did not show synergy, sequential treatments could be more effective.[18] Addressing this question will be subject of future studies.

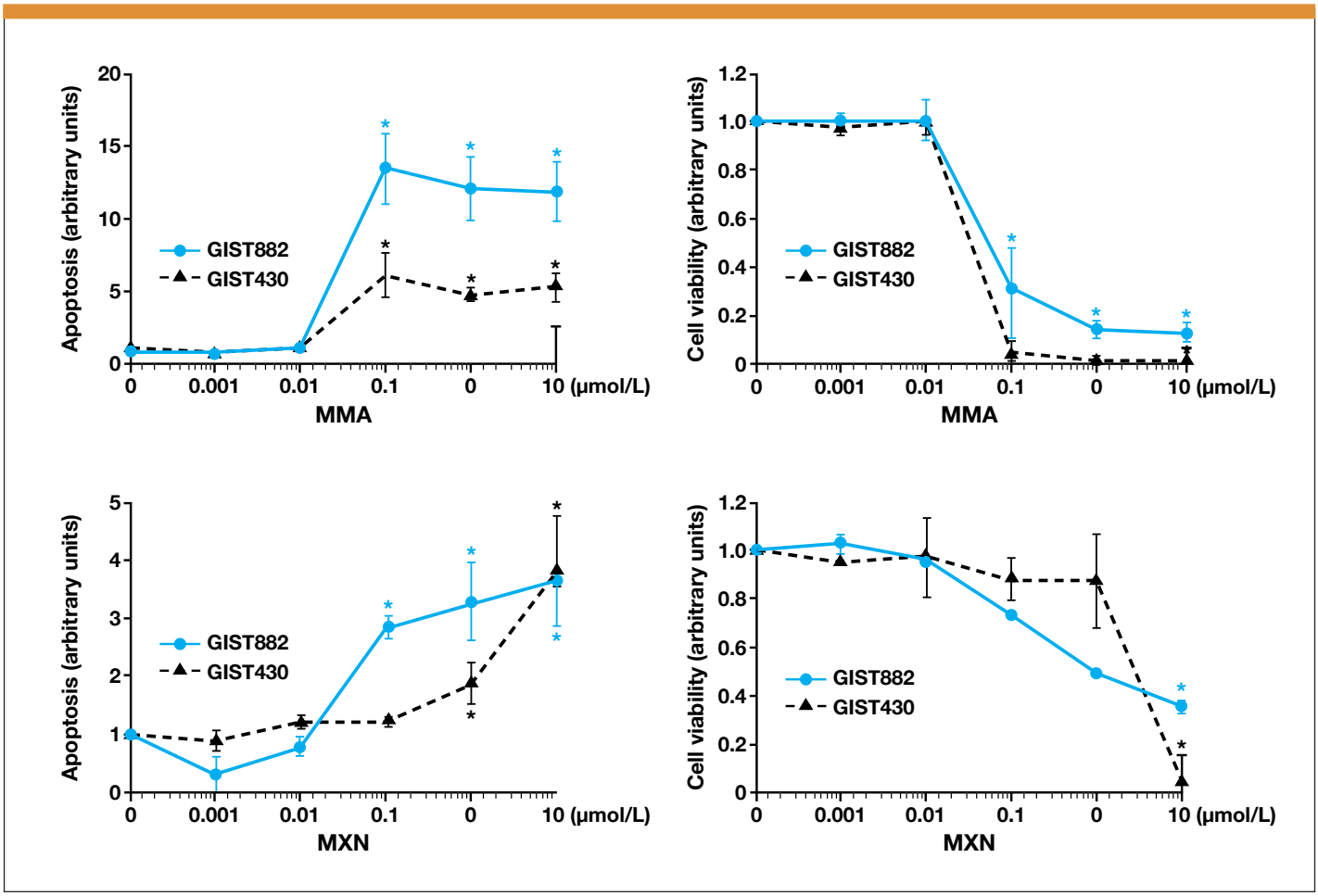

Figure 3. The transcriptional inhibitor mithramycin A (MMA) and the topoisomerase II inhibitor mitoxantrone (MXN) effectively induce time-dependent GIST cell apoptosis and cell-cycle arrest. A and B, dose-dependent effect of MMA (A) and MXN (B) on apoptosis (left) and cell viability (right) of GIST882 and GIST430 cells as measured by luminescence-based assays (mean + SE). *, $P \leq 0.05$ in comparison with control. Adapted from Ref. 14.

By revisiting the use of chemotherapeutic agents in GIST, our study has revealed an entirely new avenue for new therapeutic strategies and provided a framework for identifying drug sensitivities in GIST largely underappreciated.[14] It is key that we were able to link the activity of the chemo-therapeutic agents to intrinsic molecular requirements and defects of GIST cells, such as continued *KIT* transcription and differences in topoisomerase expression.

Targeting the DREAM Complex to Enhance Imatinib-induced Apoptosis

The search for new pathways downstream of imatinib-induced KIT inhibition has moved in some other exciting directions. One of the hurdles to effective GIST therapy is the fraction of imatinib-treated tumor cells that do not die, but instead enter the state of quiescence. These cells remain viable and can therefore serve as a reservoir for relapse and tumor progression.[19-21] Hence, one major therapeutic goal is to avoid cellular quiescence and to push as many tumor cells as possible toward apoptosis.[8]

In an earlier study, our group has reported that imatinib directly induces cell cycle exit via the APC^{CDH1}-SKP2-$p27^{Kip1}$ axis.[22] Building on these findings, we could now show that imatinib induces GIST cell quiescence *in vivo* and that this process involves the DREAM complex,[22] a newly identified key regulator of quiescence.[23]

The multiprotein DREAM complex consists of three core proteins, the pocket protein family member RBL2 (retinoblastoma related protein 2, also called p130), the E2F4 transcriptional repressor and DP (dimerization partner) as well as several regulatory proteins (LIN proteins). DREAM forms upon entry to the G0 phase of the cell division cycle, a process that is regulated by phosphorylation of the DREAM component LIN52 by the DYRK1A kinase.

We now report that upon imatinib treatment of GIST cells, activation of the DREAM complex is evidenced by up-regulation of RBL2 (p130), increased RBL2/E2F4/LIN37 complex formation and enhanced phosphorylation of LIN52.[22] Going forward, we hypothesized that interrupting this process could increase the likelihood of imatinib-induced GIST cell apoptosis. Indeed, abolishing DREAM complex formation by either siRNA or a pharmacologic agent that inhibits DYRK1A kinase activity could significantly enhance imatinib-induced GIST cell apoptosis. Another key finding of our study is that it was clearly shown that imatinib itself is able to stimulate quiescence in a subset of GIST

cells, thereby intrinsically limiting its own effectiveness.

With that in mind, more emphasis can now be put on further synthetic lethal approaches of KIT and DYRK1A inhibition to increase antitumor efficacy. Some synthetic inhibitors are already being studied and it remains to be seen whether they someday will move from the bench to the bedside.

Still, there are more open questions. What determines whether GIST cells undergo apoptosis or quiescence when treated with imatinib? Is the cell-cycle stage at the time of treatment that factor? Or, are there other mechanisms capable of mediating the switch between cell death and survival? These need to be explored. On the horizon as a possibility is that genome or transcription analyses could allow for stratification of GISTs as being prone to apoptosis or quiescence. Nevertheless, the DREAM complex appears to be a promising target to make imatinib treatment more effective in the goal of achieving complete patient responses.

Conclusion

The development of novel treatment options and biomarkers of response are beginning to show promise and could reshape strategies to address the underlying biologic basis of GIST. The potential of agents such as bortezomib, already FDA-approved in another cancer, to induce apoptosis in imatinib-resistant GIST cell lines suggests a rationale for further exploration. Results from a compound screening of already approved chemotherapeutic agents have produced some surprising results and prompted a reassessment of the role of this strategy in GIST - defying the common notion that GISTs universally respond poorly to such treatment. Additional evidence is focusing on the DREAM complex, a multiprotein complex involved in mediating GIST cell quiescence. This complex could provide a novel therapeutic target to enhance imatinib-induced apoptosis. Overall, these new avenues provide a glimpse of how treatment of GIST could be on the verge of significant advances with the hope of replicating these preclinical findings in GIST patients.

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Surgical Management, Clinical Outcomes in Rare GIST: Emerging Data Highlight Conservative Strategies, Preoperative TKI Use

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Often overlooked and presenting a challenge, and in some cases not easily detected, GIST at uncommon locations is the subject of growing interest because of its different characteristics compared to GIST at other sites. Recent reports and systematic reviews highlight the features of these rare tumors, what surgical techniques may provide a survival advantage, and delineate the role of neoadjuvant imatinib to improve outcomes.

New insights and perspectives are emerging on the importance of anatomic site as a prognostic factor in gastrointestinal stromal tumors (GISTs). Recent reports highlight some key features of these tumors and to what extent surgery can achieve favorable outcomes, particularly at locations that tend to be uncommon. GISTS are the most common sarcoma of the gastrointestinal tract, accounting for 82% of all gastrointestinal mesenchymal tumors[1,2]; management strategies for GIST in its most common locations—stomach (60-70%) and small intestine (25-30%)—are reasonably well delineated because numerous reports have established an abundant literature for these entities.

By comparison, the literature is sparse for GIST in uncommon locations; limited data exist for tumor sites that include esophagus, duodenum, and rectum and the reliability of reports is also limited by small sample size and single institution studies.[3]This picture is beginning to change, however, and so is the prognosis for patients whose tumors occur in rare locations and may be amenable to surgical excision or possible enucleation. Until recently, surgical resection appeared to confer a survival advantage but the lack of comparison subsets meant that it was unclear to what extent esophageal, duodenal, and rectal tumors could be effectively managed.

Still another issue that has also needed further clarification is the role of preoperative or postoperative imatinib in tumors arising in these uncommon locations. There has been the need to characterize the pathological and clinical response of rectal tumors, for example, to neoadjuvant imatinib. One of the poorly defined areas concerns the extent to which preoperative imatinib can shrink large rectal GISTS, thus improving the chances of sphincter preservation and decreasing the risk of considerable morbidity. The lack of data on neoadjuvant imatinib in this setting is just one piece of a much larger puzzle on the management of GIST in rare locations. As a result, much misinformation exists at a time when results from the Surveillance, Epidemiology and End Results (SEER) database show a rising incidence of GIST overall.[3]

In their report on results from the SEER database, Kukar et al highlight, for example, the conflicting data regarding the behavior of esophageal tumors and discuss implications for surgical options. Most reports have indicated aggressive behavior and poor prognosis.[4-8] There is a mixed picture regarding the role of surgery in these tumors: Blum et al[9] reported on data from 33 patients in the National Cancer Database that esophagectomy improves survival. Yet radical surgery in esophageal GIST carries an 8% mortality rate due to the associated complexity and higher morbidity associated with esophageal surgery. Again, there are conflicting data as to whether there is better or worse survival of esophageal GIST patients when compared to patients with gastric GIST. An emerging issue as well is whether enucleation is a viable option. We need clear guidelines on when local tumor enucleation is the preferred option vs primary radical surgical resection for esophageal GIST.

GIST of the Esophagus

Esophageal GIST is a very rare entity and represents less than 1% of all cases.[10] A comprehensive report by Lott et al is among the most recent studies to provide illuminating de-

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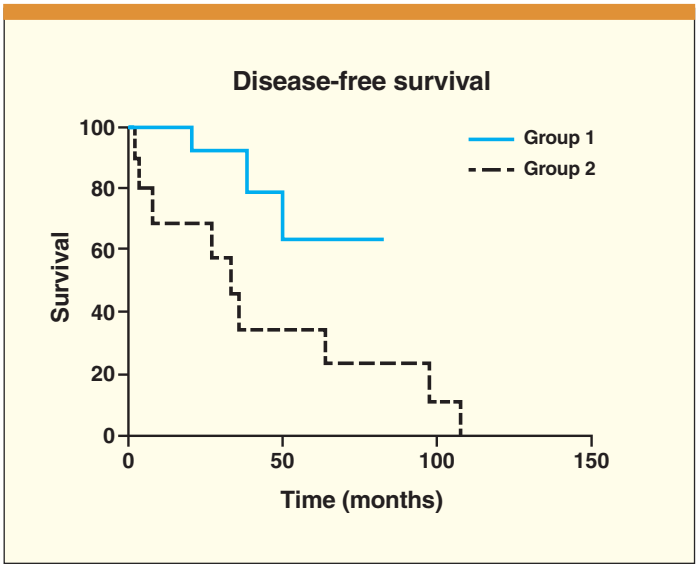

Figure 1. In a study by Tielen et al, outcomes of surgical resection were studied. Disease-free survival (DFS) was evaluated in two groups. Group 1 received imatinib before surgery. Group 2 did not receive imatinib. Median DFS was not reached in Group 1, while it was 36 months in Group 2.

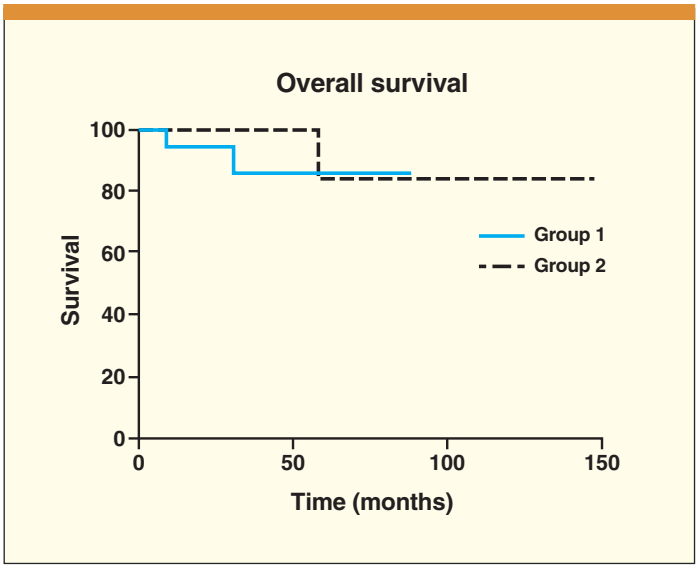

Figure 2. The study by Tielen et al also evaluated overall survival for the two groups. Median OS was not reached in both groups with a median follow-up of 39 months.

tails about this tumor's clinicopathological features and the relative merits of different surgical options. This study represents the 1argest analysis of esophageal GIST, estimating an annual incidence of 0.1 to 0.3 per million. The characteristics significantly associated with esophageal GIST include:

- An occurrence more frequent in men (P=0.035) and in patients younger than 60 at diagnosis.
- Patients with esophageal GIST present most commonly with dysphagia, weight loss, and bleeding.
- The majority show spindle cell morphology with a 100% positivity of KIT expression and 98% of CD34 expression.
- A wild type frequency of 42.9% is remarkably higher compared to GISTs from other sites.
- The high risk for metastases and unfavorable outcome with a high mortality rate is believed to be related to the large tumor size and higher mitotic rates observed in esophageal GIST.

Principles of Managing Esophageal GIST: Enucleation vs. Esophagectomy

Esophageal GISTs present unique challenges. First, the tumor must be recognized correctly as a GIST. Due to the similar clinical, endoscopic, and radiographic appearance as the far more common esophageal leiomyoma, a GIST may not be identified as such until after resection.[9]

Because GISTs are fluorodeoxyglucose (FDG) avid, FDG-positronemission tomography (PET) scanning may be used to differentiate them from leiomyoma.[11] While all GISTs in a series by Blum et al had physical characteristics noted at the time of resection that suggested they were not benign leiomyoma (poor integrity, no capsule, waxy appearance), frozen sectionwas unreliable for definitively diagnosing a GIST as this requires immunohistochemistry.[9]

The view toward the surgical management of esophageal GIST is evolving, as is highlighted by a 2015 report by Lott et al. However, the traditional view of this tumor is still largely influenced by earlier reports, including the paper by Blum et al that highlights key considerations and pitfalls in the operative theater.

Although small intestinal and gastric GISTs may be resected with segmental or wedge resections, esophageal GIST resections are essentially limited to either simple enucleation or esophagectomy. Blum et al report that in one of their cases, enucleation of a large tumor resulted in recurrence and therefore this cannot be recommended. The NCCN guidelines state that enucleation of small (2 cm or less) esopha-geal GIST may be acceptable and that small intraabdominal tumors might be resected laparoscopically, but Blum et al suggest that the poor integrity of esophageal GISTs makes thoracoscopic enucleation unadvisable.

Blum et al recommend esophagectomy for resection of larger tumors and those involving the gastroesophageal junction. For small lesions (less than 2 cm) confined to the wall of the esophagus, particularly in patients unable to tolerate esophagectomy, an open local resection may be an acceptable alternative if a margin negative resection can be obtained. However, this view was postulated more than 10 years ago and new data are emerging that call these guidelines into question.

The best surgical procedure and the optimal use of neoadjuvant imatinib for esophageal GIST have yet to be determined but the report by Lott et al provides an excellent framework with which to address issues related to appropriate choices and how some new thinking is working its way into clinical practice. Three principles of management, all linked together, are essential:

1. Appropriate pre-therapeutic histological diagnostics should be done, including biopsies.
2. Alternative surgical procedures should be considered:

radical resection vs. local tumor excision/enucleation.
3. Administration of tyrosine kinase inhibitors, primarily imatinib, as neoadjuvant, adjuvant and additive therapy.

Focusing on the relative merits of radical resection as opposed to enucleation, Lott et al used the Ulmer GIST registry in Germany consisting of 1077 cases and pooled them with case reports and case series of esophageal GIST from MEDLINE. They compared the results from these sources with 683 cases of gastric GIST from their registry. Esophageal GIST generally showed a less favorable prognosis than gastric GIST and primary tumor sizes were significantly larger , thereby resulting in a high-risk classification.

Although this study did not present specific data on surgery, the authors reviewed current guidelines and suggest criteria that could be applied to select patients for either enucleation or primary radical surgical resection. Currently, complete surgical elimination of the tumor appears to be the only curative therapeutic option in the management of non-metastatic, resectable esophageal GIST.[12] Tumor size is a key consideration in identifying which patients are more suited to one of the techniques.

The literature has not produced a consensus as yet. For example, when the goal is to achieve R0 resection by highest radicality, local tumor enucleation might be limited and primary radical surgical resection may be the treatment of choice, combined with a TKI, according to two reports.[13,14] Yet, when post-surgical morbidity and mortality are considered, local tumor enucleation is a less traumatic option , especially when comorbidities are present. According to the review by Lott, these guidelines point toward a rationale for decision making:

- Enucleation is generally recommended for smaller tumors (2 to 5 cm).
- Esophagectomy should be performed for GIST above 9 cm in size.
- For all cases with tumor between 5 cm and 9 cm, the surgical procedure chosen should be based on the patient's individual surgical risk and underlying comorbidities.

Primary duodenal GIST: Limited Resection vs Pancreaticoduodenectomy

Duodenal GISTs are relatively uncommon with several studies reporting an incidence of 3-5% of all GISTs.[15,16] Most of these tumors tend to arise from the second portion of the duodenum. Until recently, the literature was equivocal on the guidelines for this type of tumor, but as is the case with esophageal GIST, new results are beginning to resolve controversial issues and pointing toward a more conservative approach in this subset of GIST patients.

Optimal management has been controversial because unlike the approach in the stomach or small bowel where a complete resection calls for a relatively straightforward procedure, wide resections for tumors in the duodenum almost always entail a pancreaticoduodenectomy (PD) because of the complex anatomy in this area. Yet PD has been associated with a high morbidity rate,[17] and several alternative strategies have been explored : pancreas-sparing duodenectomy, segmental duodenectomy, and local resection. The trend is solidly supporting the use of limited resection as long as it is feasible as opposed to formal pancreaticoduodenectomies.[18] Nevertheless, the controversy has not been entirely settled and there remain concerns about the adequacy of margins and oncologic clearance for duodenal GISTs undergoing the limited procedure. In many cases, the choice hinges on several factors—tumor size, location (proximity to the ampulla of Vater), invasion or adherence to adjacent organs, and the patients overall health status.

Perhaps intuitively, and based on some studies with relatively small sample sizes, it would seem that LR should be the preferred technique over PD. Now, improved data, including one systematic review and another that is a retrospective analysis, are offering the kind of information to confirm that concept and better delineate the options. Compelling data emerged from two recent reports, one a systematic review and meta-analysis comparing PD with LR in this setting. Chok et al[19] focused on 11 studies, 7 of which compared 162 patients who underwent LR vs 98 who underwent PD. Those who had PD were more likely to have larger tumors (at least 5 cm) with high mitotic count, be classified as high risk and located at D2. PD was associated with a higher postoperative morbidity compared to LR.

LR was not associated with an increased local recurrence rate, had better disease-free survival and a lower rate of distant metastasis compared to PD. A key advantage to the study by Chok et al is that its pooled information offers a much better lens with which to view the relative merits of the two techniques. The conclusions reached by the study suggest several implications:

- The higher proportion of positive surgical margins associated with LR did not translate to an increase in local recurrence.
- The lower recurrence rate, better DFS, and lower rate of distant metastases could be explained by a selection bias; thus, larger and higher-risk tumors are undergoing PD and it is unlikely due to the type of resection.
- This last finding confirms other reports, which demonstrates that tumor biology and not resection type primarily determines oncologic outcome after surgical resection of GIST.

Additional evidence for the advantages of LR were presented in a French study by Duffaud et al[20] as part of a survey from 16 centers that included 114 patients from the French Sarcoma Group. As the study notes, duodenal GISTS are characterized by their complexity due to the anatomy of the pancreatic and duodenal area. However, the study found that when LR is feasible, it achieves the same rates of R0 resection, event-free survival, and overall survival as PD. The results recommend a pancreas preserving surgery as long as there are no anatomic contraindications—size or location—and there is a likelihood of achieving an R0 margin. Another advantage is the lower postoperative morbidity which in this study was 17% vs 30% for PD.

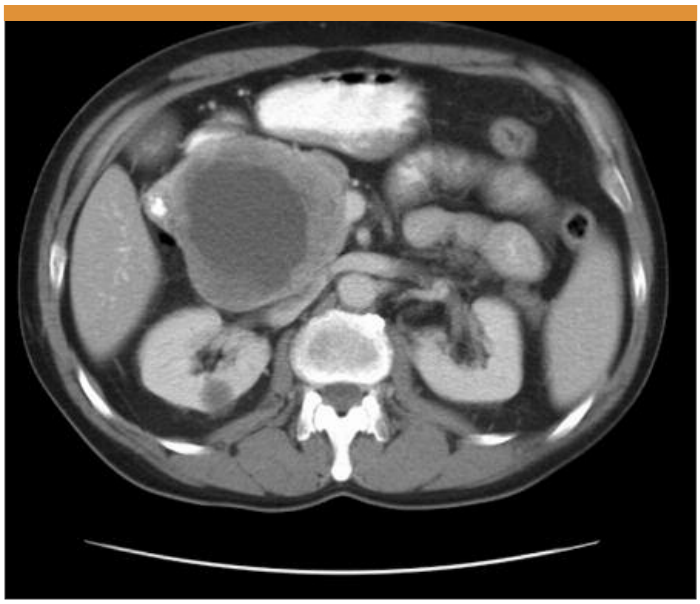

Figure 3. CT scan depicts a duodenal GIST that required a local resection.

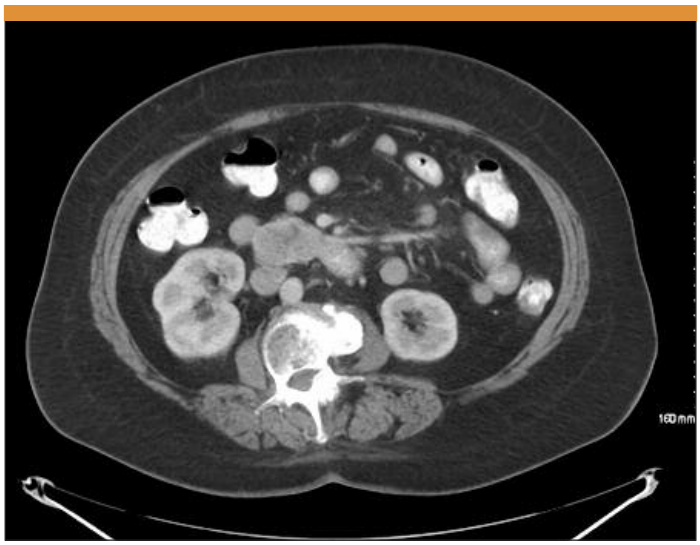

Figure 4. This scan shows a duodenal GIST that underwent a Whipple procedure.

Primary Localized Rectal/Pararectal GIST: Challenges and Management

The challenge underlying the management of rectal GIST begins with early detection, which in itself is one of the pitfalls of this rare tumor that accounts for approximately 5% of GISTs.[21] Two studies report that the diagnostic yield of endoscopic biopsy for this tumor is as low as 33.8%, owing to the fact that deeper tissue cannot be obtained with usual endoscopic biopsy forceps.

The lack of large patient series under long-term follow-up after treatment also tends to obscure the role of surgery with regard to whether this modality can achieve local control or survival. Management of rectal GIST is also problematic because of the location and size of the tumor—they are often large and bulky and confined to the pelvic space, densely adhering to the pelvic floor.[22]

Nevertheless, Tielen et al provide guidelines for surgery based on their retrospective series in 32 patients. When a rectal GIST can be freed from surrounding organs/tissues and sufficient distance from the anal verge remains, a low anterior resection with a coloanal anastomosis is possible. A formal mesorectal excision is not necessary as lymphatic metastases are rare. For lesions in the lower rectum, however, an abdominoperineal resection is often necessary to accomplish an oncological complete resection.

The location and the size of the tumor are two salient features influencing surgical options in rectal GIST. The proximity to the anal sphincter, pelvic nerves and bladder mean that an extensive surgery may be required, as noted by Tielen but also noted by Huynh et al. Despite these issues, conservative surgical procedures and approaches may be considered, including local excision, anterior resection, trans-sacral/anal/vaginal approaches, and laparoscopic strategies.[23-25] Ultimately, the choice is generally dependent on tumor size and location in relation to the anorectal margin. In the series by Huynh et al,[26] resections with clear margins (R0 resections) were more common when abdominoperineal resection was used vs conservative surgery (8/11 vs 14/30). Yet tumor recurrence was similar in both groups. Although a prospective study is lacking, there is one report suggesting that there is no difference in survival rates between the conservative vs radical approach. Unlike the emerging data in esophageal and duodenal GIST, there appears to be less of a consensus in the literature with regard to management of rectal GIST, although Huynh et al propose that local resection should be performed if microscopically clear margins can be achieved.

Neoadjuvant Imatinib: A Game-Changing Strategy

Imatinib treatment for rare GIST is not only feasible, safe, and effective, it could have a remarkably potent effect on changing and optimizing surgical outcomes for this tumor. There is abundant literature on how this TKI has an important role in downsizing large rectal GIST and in reducing the mitotic activity. There is additional evidence that it could also play an important role in the surgical management of esophageal and duodenal GIST, perhaps facilitating the use of conservative approaches.

The potential in rectal GIST is particularly advantageous for imatinib. Machlenkin et al[27] offer this view: because these tumors are in the vicinity of pelvic structures, such as the bladder and anal sphincter, and given that radical surgery may lead to considerable morbidity, downsizing could change the surgical approach and permit less invasive surgery. Although this Israeli study was relatively small, it highlighted in 12 patients how imatinib could prove efficacious. With neoadjuvant imatinib, one patient had a complete clinical response, 6 had a partial response, and 2 had stable disease. In the 7 patients who then underwent surgery, 6 had an R0 resection and 1 had an R1 resection; 3 patients had recurrence and there was no disease-related mortality. The authors noted a significant reduction in tumor size and

mitotic activity during preoperative imatinib.

Preoperative imatinib therapy was administered to 12 (30%) of the patients in this series because of large GISTs, difficulty of complete tumor removal, and preservation of the anal sphincters. In all cases, it enabled a modification in tumor size and/or density. It also permitted the performance of conservative surgery in 8 of 12 patients (6 of these 8 tumors were located in the lower third of the rectum). Thus, this treatment was feasible, safe, and effective. Since 2005, several case reports or small series regarding the use of preoperative imatinib treatment for rectal GISTs have been published. All concluded that preoperative imatinib therapy has an important role in downsizing large rectal GISTs and in reducing the mitotic activity. Because these tumors are in the vicinity of pelvic structures (i.e., bladder, major pelvic nerves, and anal sphincters) and given that radical surgery may lead to considerable morbidity, downstaging might be beneficial in this situation, allowing function-sparing procedures and less invasive surgery while potentially improving tumor resectability. Preoperative treatment is thus a reasonable option for patients with locally advanced rectal GISTs that require abdominoperineal or multivisceral resection for complete tumor removal.

Controversy remains, however, regarding the optimal duration of preoperative therapy. Patients in the Machlenkin study received preoperative imatinib for a median duration of 7 months (range, 2–10 months). In the EORTC phase III trial, the median time to best response was 4 months, but some responses were documented later . Similar observations have been made in case reports of preoperative imatinib in localized diseases. Therefore, it would be reasonable to plan a final surgery within 6 to 12 months of imatinib onset.

Interestingly in the series by Machlenkin, 18 patients (72%) in the non-imatinib group and only 2 (16%) in the imatinib group developed local recurrence. The study showed that preoperative and/or postoperative imatinib significantly reduced the risk of not only local recurrence ($P = 0.006$), but also overall relapse ($P = 0.011$), and significantly improved the disease-free survival with no impact on overall survival.

Duodenal GIST and Imatinib

Although the data appear less compelling than the use of imatinib in rectal GIST, its administration in duodenal GIST also yields benefit. Hoeppner et al used imatinib for downstaging of the tumors in 2 patients because large duodenal GIST infiltrating adjacent organs or large vessels made the possibility of a complete resection questionable. In reviewing the results of various studies, Hoeppner et al[28] noted pathologic response rates as high as 86% and a rate of complete resections after treatment with imatinib of 89%. The findings were impressive in the series of patients in the Hoeppner study: in case of high-risk duodenal GIST with a >30% risk of recurrence or microscopically margin-positive resection, adjuvant imatinib treatment was also carried out. None of the patients treated with imatinib before or after surgery had recurrent disease.

Similar conclusions emerged from the retrospective report by Duffaud et al who also benefit with adjuvant imatinib in their high-risk duodenal GIST patients. They found that the TKI achieved a possible impact on the outcome in this subset, confirming data from previous reports. In view of these findings and others showing a benefit of imatinib, the recommendation of adjuvant imatinib for 3 years is now a standard of care for patients with high-risk GIST at any site. However, the Duffaud analysis, the median duration of adjuvant imatinib was short and the number of patients was limited. If neoadjuvant imatinib could downstage tumors, particularly those that might require extensive surgery, its use in patients with duodenal GIST could potentially allow a proportion of patients who would otherwise require a PD to undergo LR instead.

Imatinib and Esophageal GIST

Because of the potentially high morbidity of esophagectomy and the relative lack of a substantial barrier to local extension that makes complete resection difficult, imatinib should be considered as neoadjuvant therapy for larger tumors. Cytoreduction may decrease the risk of tumor rupture and increase the likelihood of potentially curative complete resection. Whether to use imatinib as a neoadjuvant agent prior to planned resection or to use resection as salvage therapy after imatinib failure has yet to be established.

Conclusion

Although rare, GIST arising in uncommon locations has been a new focus of reports published within the last few years. GIST of the esophagus, duodenum, and rectum present a different set of challenges compared with tumors elsewhere in the gastrointestinal tract and should prompt efforts of early detection. The anatomic location of these tumors, particularly rectal GIST, can be problematic for surgery, but improved oncologic outcomes have been achieved with the use of limited resection. The use of neoadjuvant imatinib has had an impact on downstaging of GIST and improving the likelihood of conservative surgery achieving a favorable outcome and limiting recurrence.

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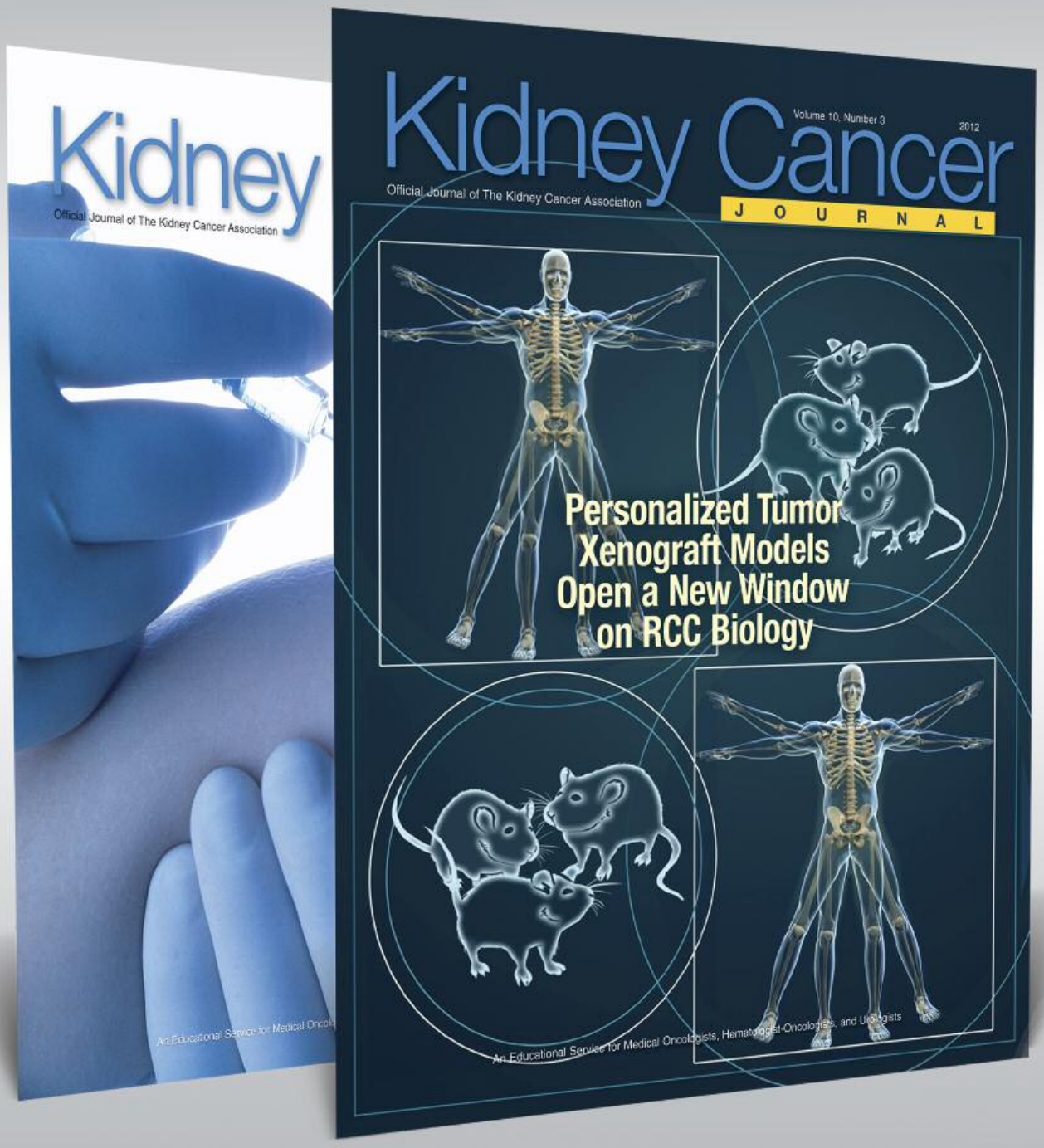

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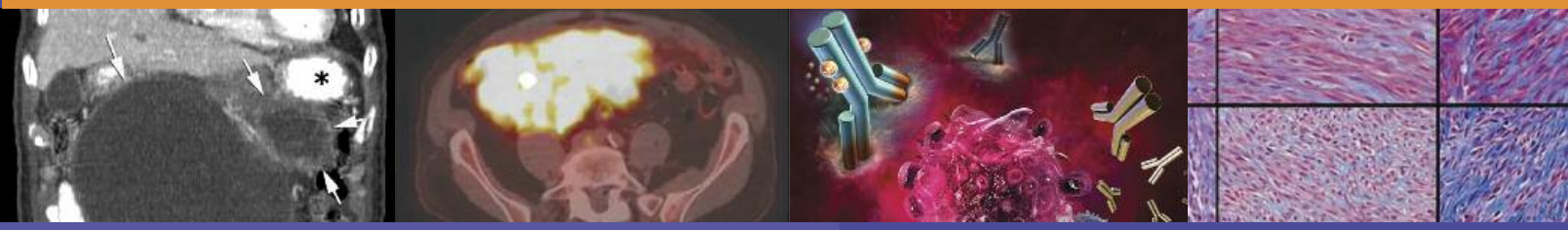

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