

Considering the role of radiation therapy for gastrointestinal stromal tumor

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Abstract: Gastrointestinal stromal tumors (GISTs) are rare mesenchymal tumors arising in the gastrointestinal tract. Over the last decade, the management and prognosis of GISTs has changed dramatically with molecular characterization of the *c-kit* mutation and the adoption of targeted systemic therapy. Currently, the standard of care for resectable tumors is surgery, followed by adjuvant imatinib for tumors at high risk for recurrence. Inoperable or metastatic tumors are treated primarily with imatinib. Despite excellent initial response rates, resistance to targeted therapy has emerged as a common clinical problem, with relatively few therapeutic solutions. While the treatment of GISTs does not commonly include radiotherapy, radiation therapy could be a valuable contributing modality. Several case reports indicate that radiation can control locally progressive, drug-resistant disease. Further study is necessary to define whether radiation could potentially prevent or delay the onset of drug resistance, or improve outcomes when given in combination with imatinib.

Keywords: GIST, imatinib, radiotherapy

Background

With an estimated 4,000–6,000 cases per year in the US,¹ gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumor of the gastrointestinal tract.² GISTs originate from the interstitial cells of Cajal, an intestinal pacemaker cell in the gut.³ GISTs most often arise in the stomach or small intestine. The presentation of GISTs varies depending on the clinical site and size. Small tumors may be detected incidentally,⁴ while larger tumors often present with pain, bleeding, or anemia, or bowel obstruction.⁵

Previously, the diagnosis of GISTs relied on tumor morphology alone, when inconsistencies and ambiguity were relatively common.⁶ This method of diagnosis changed after molecular characterization identified a near universal gain of function mutation in the *c-kit* gene, which encodes a proto-oncogenic tyrosine kinase,⁷ driving the malignant behavior of the GISTs. The *KIT* gene product is involved in signaling for cell survival, proliferation, and differentiation.⁸ GISTs not expressing the *KIT* mutation often have mutations in the gene encoding platelet-derived growth factor receptor alpha (PDGFRA).⁹ These two mutations account for approximately 90% of mutations.¹⁰ Tumors expressing either of these mutations are indistinguishable with respect to the activation of downstream signaling activation and cytogenetic changes.⁹ The enhanced understanding of tumor pathogenesis has dramatically changed the treatment and prognosis of GISTs, as the mutation characterization has facilitated targeted therapy with selective tyrosine kinase inhibitors (TKIs). Prior to targeted

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therapy, surgical resection was the only effective treatment for GISTs, and even resected tumors demonstrated high recurrence rates.

Imatinib, originally approved for the treatment for chronic myeloid leukemia (CML), is a small molecule TKI. The drug selectively inhibits the enzymatic activity of several tyrosine kinase receptors, including c-kit and PDGFRA. The value of imatinib in GISTs was first widely reported in 2001 with a case report showing marked, prolonged clinical response in a woman with metastatic disease.¹¹ Since then, randomized data have supported TKI therapy in the metastatic^{12–14} and adjuvant setting for high-risk tumor.^{15–17} Imatinib is now considered standard adjuvant therapy for tumors considered at high risk for recurrence, and is used upfront for metastatic or locally advanced, unresectable tumors.

Treatment in the imatinib era

Historically, surgery was the only effective therapy, with a 5-year survival of 42% in patients with complete resection, compared with 9% for incomplete excision.¹⁸ The majority of tumors with localized presentations could be resected, but overall outcomes were unsatisfactory due to the high risk of recurrence.¹⁹ In the pre-imatinib era, roughly 50% of patients relapsed after resection, predominantly intra-abdominally, at the primary site, peritoneum, and/or liver. High-risk tumors, such as those with size greater than 5 cm and >5 mitosis/50 high-powered field (HPF), recurred more than 50% of the time within 2 years.^{19,20} Traditional chemotherapy did not improve outcomes for resected or recurrent disease. Thus, surgery alone did not offer long-term survival for many patients.

Significant improvements in outcomes occurred with the recognition of mutational activation of the *KIT* gene and the advent of TKI therapy. Randomized data support an improvement in progression-free survival (PFS) with adjuvant therapy for resected tumors >3 cm in size,¹⁵ with the greatest benefit for high-risk tumors. Patients with high-risk tumors, as defined by the modified consensus criteria, consisting of tumor size >10 cm, mitotic count >10/50 HPF, size >5 with mitotic rate >5/HPF, or tumor rupture before or at surgery, demonstrated an overall survival and recurrence free survival advantage with 36 months of imatinib.¹⁶ Currently, adjuvant imatinib is recommended for patients with a nomogram estimated risk of recurrence >50%,²¹ size >5 cm, mitotic count >5/50 HPF, and/or with tumor rupture.²² Additional studies are ongoing to determine whether longer durations of therapy are of benefit, since trials have demonstrated high rates of recurrence shortly after discontinuation of

imatinib.¹⁶ Nevertheless, median survival in the imatinib era is greatly improved, at 11.7 years in one cohort of nearly 1,200 patients.²³

Imatinib has also changed the management of metastatic or locally advanced GISTs. Neoadjuvant imatinib can make an inoperable tumor resectable, or improve the likelihood of organ preservation in some circumstances.²⁴ For metastatic disease, survival outcomes have vastly improved. Patients with metastatic disease at presentation can now expect a median survival in excess of 6 years.²³

Limitations of imatinib therapy

Despite the improvements in survival and progression observed in the imatinib era, recurrence remains a significant problem. Patterns of recurrence analysis in the American College of Surgeons Oncology Group (ACOSOG) Z9000 trial indicated a 5-year relapse free survival of 40%, with local only recurrence occurring in as many as 33%.²⁵ Although high response rates are achieved in metastatic or advanced GISTs, complete response rates are rare, at <10%. Non-viable appearing tumor masses often contain viable cancer cells,²⁶ suggesting that imatinib is not cytotoxic and ongoing therapy is needed to maintain the benefit. Randomized trials show a marked increase in recurrence when the drug is discontinued²⁷ implying a “cytostatic” drug effect. High rates of recurrence noted after discontinuing the drug may suggest a delay, rather than prevention of recurrence. For example, in advanced GISTs, Le Cesne et al demonstrated that discontinuation after 3 years of continuous therapy resulted in a 2-year PFS of 16%.²⁸ Additionally, the shape of relapse free survival curves in adjuvant trials, which drop within 2–3 years from the end of adjuvant therapy, lend further support that the increase in survival could be attributable to a delay in progression, rather than increase in cure.²⁹

Resistance to targeted therapy is an emerging clinical problem. In the metastatic setting, the standard duration of therapy is indefinite until the development of imatinib resistance. While only 10%–15% of patients will have primary insensitivity to imatinib,³⁰ secondary resistance affects 50% by 2 years.³¹ Therapeutic options remain limited after resistance. A minority of patients will have further response to increased doses of imatinib.^{13,32} Alternative TKI therapy with multi-targeted agents, such as sunitinib or regorafenib, offers low objective response rates,^{33,34} and improvements in PFS are of a much shorter duration. Further acquisition of mutations leading to subsequent resistance to sunitinib is a known clinical problem.³⁵ Thus, TKI therapy and/or imatinib rechallenge are options, yet limited efficacy suggests that

secondary resistance has created a therapeutic challenge for a significant number of GIST patients.

Tolerance of imatinib is another important consideration. Grade 3 toxicity affects as many as 25%–35% of patients, and includes diarrhea, muscle cramps, and edema, with increased rates of side effects reported for longer durations of therapy. Discontinuation rates, unrelated to GIST recurrence, of 26% have been reported with 36 months of adjuvant therapy.¹⁶ This is in comparison to the 13% among patients assigned to 12 months of treatment. For a therapy that may be recommended for several years, it would be of interest to investigate avenues to improve tolerability of imatinib, or reduce the overall treatment duration.

Mechanisms of resistance to imatinib

Evidence supports secondary mutations as a source of recurrent disease.³¹ Novel additional mutations of the *KIT* gene have been implicated in the development of imatinib-resistant GISTs.³⁶ Residual microscopic clones may represent cells having acquired mutations during therapy or expression of inherent heterogeneity within the cells. Clonal heterogeneity and clonal evolution, particularly under the selection pressure of therapy, are recognized as a pattern of resistance development in many types of tumors.³⁷ Follow-up amongst GIST patients with careful imaging demonstrate a “resistant clonal nodule” recurrence pattern in which a new enhancing focus of growth can appear within a pre-existing tumor mass in more than half of those with recurrence.^{38,39} Molecular analysis confirms that new mutations in *KIT* and *PDGFRA* occur in 80% of recurrent nodules biopsied. The nodule growth within the original tumor supports the idea of clonal evolution from the original tumor. Both inherent tumor heterogeneity and the acquisition of mutations could explain why a single-targeted therapy is unlikely to control disease in the long term. Development of resistance is commonly observed with chronic targeted therapy for other solid tumors, with ongoing research aimed at strategies to overcome resistance.⁴⁰

Long-term imatinib therapy, which can lead to the selection of resistant clones, adds a layer of complexity to the design of further salvage therapy. Because each tumor nodule may undergo individual genetic selection of mutations in the *KIT* oncogene, further additional targeted therapy becomes more difficult. Alternatively, the development of locally resistant clones suggests that management with an alternative therapy, perhaps combined with imatinib, may have a role in either limiting or overcoming resistance in the ongoing management of GIST patients.

The rationale for radiation therapy (RT)

Historically, RT has not often been considered for GISTs. The gastrointestinal location and patterns of spread would potentially require large abdominal fields, presenting a narrow therapeutic window due to the dose tolerances of the small bowel to radiation. As such, there has been little investigation into the efficacy of RT.

There exist several potential scenarios where RT could provide benefit in the management of GISTs. In general, certain local therapies that are directed to resistant nodules can provide alternative avenues that do not rely on a specific molecular pathway. For example, local therapy with radiofrequency ablation has been shown to be an effective and safe treatment option for patients with limited clonal resistance.^{41,42} If given adjuvantly prior to failure, RT could potentially limit the development of resistance and serve as an important adjunct to imatinib. For tumors at high risk of local recurrence or R1 resection, preoperative RT could be considered, potentially with imatinib, for cytoreductive effect. A preoperative approach could allow for increased sparing of normal tissue from radiation in comparison to postoperative radiation and allow for safer dose escalation. Additionally, radiotherapy may be a local treatment option for patients with tumors that are surgically inaccessible due to location, or in whom resection would lead to severe functional impairment, such as duodenal or esophageal locations. Finally, RT can be used for palliation of local symptoms. In the setting of locally progressive and/or metastatic GISTs, short courses of RT have been shown to be effective for tumor control and symptom management, with low rates of toxicity.^{43–46}

A number of publications provide insight into the efficacy of RT. In the largest published series, Cuaron et al reported local control in 15 of 17 treated lesions.⁴⁵ Patients were most commonly treated with palliative intent after TKI failure with 30 Gy at 3 Gy/fraction, with concurrent TKIs administered in 41%. The rate of partial radiographic response was 35%, and the 6-month local PFS was 57%. Of note, patients treated with a dose per fraction >5 Gy (n=8) had a radiographic response rate of 63%, suggesting that GISTs are more sensitive to a higher radiation dose. Knowlton et al reported 20 years of durable local control in a 37-year-old man treated in the pre-imatinib era with debulking surgery and 36 Gy for an unresectable, non-metastatic GIST.⁴⁷ Similarly, local control was reported in six of nine patients treated with 45–60 Gy of radiation for incompletely resected disease in the pre-imatinib era.⁴⁸ Radiation, when administered to a woman with progressive GIST, helped promote local tumor control to several sites of metastatic disease in tandem with other local and systemic therapies, and

potentially prolonged survival despite disseminated disease.⁵⁰ Postoperative radiation consisting of 50.4 Gy was administered following a R1 resection of a 7 cm rectal GIST. Two years later, the patient remained free of disease.⁵¹

A few case studies have addressed concurrent radiotherapy and TKIs. Fifty Gy directed at a large supraclavicular metastasis, in combination with sorafenib, resulted in a clinical and radiographic response, and the treated tumor remained stable despite the eventual progression of other metastatic sites.⁵² Similarly, when radiation and imatinib were used together for the treatment of a large, incompletely resected pelvic mass, the mass regressed completely and remained locally controlled, despite the growth of a liver metastasis.⁵³ The control of tumor at the locally treated sites, with progression at the sites of metastasis while on TKIs, suggests that radiation helped eradicate resistant clones. Radiotherapy, combined with imatinib, was effective in shrinking a large, rectal GIST, enabling a sphincter-sparing surgery without major perioperative morbidity. A pathologic complete response was achieved with a dose of 50.4 Gy.⁵⁴ This further supports the potential role for radiation in locally advanced GISTs that are technically unresectable.

Historically, abdominal radiation has posed technical challenges due to dose-limiting toxicities of the small bowel and visceral structures. In recent years, intensity-modulated RT (IMRT) and other technological advances have improved the therapeutic ratio of abdominal RT, allowing for dose escalation and potential reduction in acute and delayed toxicity by facilitating treatment delivery and normal tissue protection.⁵⁵ Adjacent bowel does continue to limit the ability to deliver high radiation doses, yet long-term GIST control is possible with moderate doses, suggesting that treatment is feasible in a variety of circumstances. Further, simultaneous integrated boost (SIB) techniques can allow for radiation “dose painting,” with lower doses at the edges of treated volumes, adjacent to critical structures. With modern advanced treatment planning, abdominal radiation is associated with mild-to-moderate acute toxicity, with a relatively low potential for serious delayed complications.⁵⁶

Future directions

Local control is of paramount importance for patients with GISTs. However, in-tumor nodular recurrence,³⁹ and resistance to imatinib, pose serious clinical challenges. Aside from the impact on overall outcomes, local failure can be associated with pain, bleeding, and other potentially threatening symptoms, for which a local treatment could be helpful. The rationale to treat a limited number of metastatic or recurrent sites of disease has

been recently reviewed.⁵⁷ This state of “oligometastasis” or “oligo-recurrence” may be ideal for the addition of localized therapy, potentially in combination with imatinib. As radiation is not reliant on mutation-specific responses, the addition of radiation in this setting could eradicate emergent resistant clones, while continued imatinib therapy can continue to treat sensitive clones. In this circumstance, the additional local radiotherapy could result in long-term control or cure.

Although rationale exists to support radiation in the management of GISTs, supportive evidence is limited to small case series and case reports, and additional study is needed. Future trials should address the role of radiation to either limit the development of imatinib resistance, or to eradicate limited sites of nodular local tumor growth or distant recurrence. Additionally, radiation should also be tested in the locally advanced, unresectable setting, where it may facilitate resection. Study designs should include investigation into the safety of concurrent radiotherapy with imatinib, and the ideal dose of radiotherapy for GISTs.

Conclusion

GISTs are rare intra-abdominal tumors, which are typically treated with resection and adjuvant imatinib if at high risk for recurrence, or imatinib alone if unresectable. Imatinib has prolonged the survival of patients with GISTs. However, ongoing therapy is necessary, responses are rarely complete, and the development of imatinib resistance and treatment-related toxicity are not uncommon. There are currently few durable, efficacious treatment options after imatinib failure. Radiation has an established role in the management of many other cancers for local control, and may be underutilized for GISTs, given the mechanistic rationale and support from case studies. RT has the potential to eradicate imatinib resistant clones, downstage unresectable disease, and palliate symptoms related to local progression. Further study is warranted to establish the role of RT in the multidisciplinary management of GISTs.

Disclosure

The authors report no conflicts of interest in this work.

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