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Analysis of Prognostic Factors Impacting Oncologic Outcomes After Neoadjuvant Tyrosine Kinase Inhibitor Therapy for Gastrointestinal Stromal Tumors

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Abstract

Background—Management of gastrointestinal stromal tumors (GISTs) has been transformed with tyrosine kinase inhibitors (TKIs). While data on optimal duration of adjuvant imatinib remains elusive, guidelines for administration of neoadjuvant TKIs remain unknown.

Methods—Under an institutional review board-approved protocol, patients at our institution with a diagnosis of GIST treated with neoadjuvant TKIs and surgical resection were identified. Clinical and pathologic characteristics were obtained from medical records.

Results—Ninety-three patients underwent surgical resection after neoadjuvant TKI therapy; 41 had primary and 52 had recurrent/metastatic GIST. Median follow-up was 2.4 years. Median duration of neoadjuvant therapy was 315 (range 3–1,611) days for primary and 537 (range 4–3,257) days for recurrent/metastatic GIST ($p = 0.001$). Two-year, recurrence-free survival (RFS) was 85 and 44 % for primary and recurrent/metastatic disease, respectively, whereas 2-year overall survival (OS) was 97 % for primary and 73 % for recurrent/metastatic GIST. For primary GIST, duration of neoadjuvant therapy >365 days ($p = 0.02$) was associated with higher risk of

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recurrence on univariate analysis, whereas none of the clinicopathologic factors impacted OS. For recurrent/metastatic disease, disease progression was associated with a shorter OS ($p = 0.001$), but no factors were found to impact RFS. Lastly, when examining all patients, KIT mutations ($p = 0.03$) and multivisceral resection ($p = 0.011$) predicted shorter RFS.

Conclusions—Neoadjuvant TKIs can be effectively used for the treatment of primary and recurrent/metastatic GIST. While duration of neoadjuvant therapy, KIT mutation status, and the need for multivisceral resection can help to predict higher risk for recurrence, progression on neoadjuvant TKIs can aid in selection of patients with recurrent/metastatic disease for surgical resection.

The hallmark of gastrointestinal stromal tumors (GISTs) is the presence and activation of the tyrosine kinase cKIT.^{1,2} Identification of differential expression in >90 % of GISTs presented a unique subset of sarcomas that could be targeted with tyrosine kinase inhibitors (TKIs).² Significant improvements in disease-free and overall survival (OS) have been reported for patients with high-risk GIST treated with imatinib mesylate.^{3–5} The success of this treatment in a tumor notoriously resistant to standard chemotherapies was unprecedented and led to subsequent studies confirming its efficacy.^{6–8}

Having established a role for imatinib in adjuvant treatment of high risk GIST, the concept of employing this targeted therapy in the preoperative setting has become the subject of recent studies.^{8–11} GISTs can present in various locations along the gastrointestinal tract, and while resection in some sites is feasible without significant morbidity, reduction in tumor size in the esophagus, duodenum, and rectum from neoadjuvant therapy could substantially alter the operation and associated morbidity.² In addition to tumor downsizing, potential benefits of neoadjuvant treatment for GIST include in situ measurement of drug sensitivity, early treatment of microscopic metastases, and the opportunity to assess tumor biology.

The effect of preoperative imatinib for patients with GIST has been examined in short-term preoperative therapy trials, resulting in measurable radiographic response in more than 60 % of patients and incrementally increased cell death with increased duration of therapy.¹² The concept of neoadjuvant treatment for locally advanced or metastatic/recurrent GIST was studied in a prospective manner by the RTOG incorporating 2 months of neoadjuvant therapy followed by 2 years of adjuvant therapy after surgery. There were no significant effects on surgical morbidity and 5-year, progression-free survival of 57 and 77 % and OS of 30 and 68 % for patients with metastatic/recurrent and primary tumors, respectively, were recently reported.⁸ These results and others demonstrate that a neoadjuvant treatment approach is safe and can be associated with acceptable oncologic outcomes.

The purpose of this study was to review our experience with neoadjuvant therapy for GIST to determine if disease characteristics, systemic treatment considerations, or surgical variables can serve as prognostic factors to guide the management of these complex patients.

METHODS

Following institutional review board approval, we reviewed GIST patients treated at the University of Texas MD Anderson Cancer Center from 2000 through 2012. The study was limited to patients who received neoadjuvant TKI therapy and had surgical resection. Patients with primary, locally recurrent, or metastatic disease were included. Charts were reviewed for information on tumor characteristics, neoadjuvant and adjuvant treatment, surgical management, and time to recurrence or death.

Definitions

We defined neoadjuvant therapy as treatment with any TKIs preoperatively, including imatinib mesylate, sunitinib, nilotinib, and dasatinib. Patients who received multiple TKIs regardless of reason (i.e., adverse effects or lack of therapeutic response) were categorized as having >1 TKI. Multivisceral resection was defined as surgery encompassing resection of multiple anatomic sites (i.e., partial gastrectomy with splenectomy and distal pancreatectomy). Patients were considered to have multivisceral resections if they had multifocal metastases involving >1 organ site resected, such as surgical excision of a peritoneal nodule requiring small-bowel resection and a partial hepatectomy for liver metastases. KIT mutations were classified as wild-type, exons 9, 11, 13, or 17. Patients with exon 11 and another mutation were grouped with the patients with exons 9, 13, or 17 mutations. Only one patient had a PDGFRA mutation and so it was not included in the analysis. Progression was defined as growth in any tumor measured by radiographic imaging or development of new tumors during neoadjuvant treatment. Recurrence-free survival (RFS) was calculated from the date of surgery to documented disease recurrence. OS was calculated from the date of surgery until death or last follow-up.

Statistical Analysis

Patient, tumor, and treatment characteristics were evaluated and compared between primary and recurrent/metastatic tumors. The Wilcoxon rank-sum test or Student's *t* test was used to compare means of continuous variables. The χ^2 test or Fisher's exact test was used for univariate comparison of categorical variables. Kaplan–Meier survival curves were calculated, and the log-rank test used to compare OS and RFS between groups. Stata and IBM SPSS statistical software (SE 10.1, StataCorp, College Station, TX and IBM SPSS Version 21, Armonk, NY) were used for analyses. All *p* values were two-tailed, and *p* < 0.05 was considered significant.

RESULTS

Patient Characteristics

During the study period, 77 patients with GIST were treated with neoadjuvant TKI and subsequently underwent surgical resection. This included 93 cases, as several patients developed recurrence or metastases and were treated a second or third time with neoadjuvant therapy and surgery. Of the 93 cases, 41 were patients with primary GIST and 52 with locally recurrent/metastatic disease (Table 1). Median age for patients with primary disease was 62.5 years (range 28–88) and for recurrent/metastatic disease was 60 years (range 36–

75; $p = 0.1$). The majority were male (63.4 % primary and 67.3 % recurrent/metastatic; $p = 0.8$). Median tumor size at presentation was 8.4 cm (range 2.9–21) for primary and 8.2 cm (range 0.8–31) for recurrent/metastatic disease ($p = 0.4$). There were more patients in the primary tumor cohort having gastric GIST (65.9 %) compared with recurrent/metastatic GIST where small bowel tumors were more common (30.8 %; $p = 0.001$; Table 1).

KIT Mutations

The knowledge regarding KIT exon mutations was in evolution throughout the study period. As a result, in our cohort, KIT mutation status was tested in 75 patients (80.6 %). Of the 34 patients with primary disease and known KIT mutation status, 26 (76.5 %) had exon 11 mutations, 3 (8.8 %) had a mutation in other exons (9, 13, or 17), and 5 (14.7 %) were wild-type. In the 41 patients with recurrent/metastatic tumors, 28 (68.3 %) had exon 11 mutations, 7 (17.1 %) had mutations in exons 9, 13, or 17, and 6 (14.6 %) were wild-type (Table 1). There was no statistically significant difference in mutation status between primary versus recurrent/metastatic disease ($p = 0.6$). The distribution of KIT mutations is similar to previously published rates, with exon 11 mutations being most common.¹³

Neoadjuvant Treatments

In evaluating neoadjuvant treatment regimens in our patient cohort, several variables were significantly different when comparing patients with primary GIST versus those with recurrent/metastatic disease. Patients with recurrent/ metastatic GIST were more likely to be treated with multiple TKIs (38.5 vs. 0 %, $p < 0.0001$), require dose escalation (42.3 vs. 0 %, $p < 0.0001$), and be treated for a longer duration before surgery >537 days (range 43–3,257) vs. median 315 days (range 3–1,611), $p = 0.001$; Table 2]. Similarly, the incidence of disease progression was greater in patients with recurrent/metastatic GIST than those with primary GIST (58.8 vs. 2.4 %, respectively, $p < 0.0001$; Table 2).

Surgical Outcomes

For patients undergoing neoadjuvant treatment for primary GIST, complete tumor extirpation required multivisceral resection in 14 (34.1 %), whereas 24 (46.2 %) of those with recurrent/metastatic disease required multivisceral resection ($p = 0.3$; Table 2). The incidence of positive margins (either R1 or R2 resections) was low with 2 (4.9 %) and 4 (7.7 %) patients with positive margins on final pathology in primary and recurrent/metastatic disease, respectively (Table 2).

RFS and OS

The median follow-up for all patients was 2.4 years (range 0.05–10.3); 3.0 years (range 0.05–8.6) in the primary GIST cohort and 2.0 years (range 0.06–10.3) in the recurrent/ metastatic cohort. For patients with primary GIST, the actuarial 2-year RFS and OS was 85 and 97 %, respectively. Patients with recurrent/metastatic GIST had worse RFS and OS (44 and 73 %, respectively; Fig. 1). For primary GIST, nearly 83 % received TKIs in the adjuvant setting following surgical resection for a median duration of 657 days (range 34–1,479). In the recurrent/metastatic cohort, more than 90 % continued TKI therapy after surgical resection.

Factors Associated with Recurrence and OS

Univariate analysis was conducted to identify disease characteristics, treatment-related factors, or surgical factors that impacted oncologic outcomes following neoadjuvant therapy. For patients with primary tumors, variables selected included KIT mutation status, duration of neoadjuvant therapy (>365 vs. ≤365 days), need for multivisceral resection, and pathologic margin status (negative vs. positive). For recurrent/metastatic patients, the same variables were examined together with dose escalation, number of neoadjuvant TKIs, and progression on therapy. Kaplan–Meier curves were generated, and the log-rank test was used to compare groups. Given the rarity of certain KIT mutations, exons 9, 13, or 17 mutations were grouped for the purpose of statistical analysis (Fig. 2; Supplementary Fig. 1).

For primary tumors, only duration of therapy impacted RFS, demonstrating that patients with prolonged neoadjuvant therapy (>365 days) had a higher risk for recurrence ($p = 0.02$; Fig. 2). We assessed additional time points, and with shorter time intervals the RFS curves merged closer together (data not shown). Despite this, the difference was still significant between >270 and ≤270 days, suggesting that the optimal duration of therapy may be 9–12 months for primary GIST. While multivisceral resection did not reach statistical significance in this group, there was a trend toward shorter RFS ($p = 0.069$; Fig. 2).

In the patients with metastatic/recurrent GIST, none of the variables examined impacted RFS (Supplementary Fig. 1). There was a trend toward significance for patients who progressed on neoadjuvant treatment ($p = 0.072$; Fig. 2).

In regards to OS, for primary GIST, no factors were identified to impact patient outcome. However, for patients with recurrent/metastatic GIST, progression during neoadjuvant therapy was a significant factor in predicting lower OS following surgery ($p = 0.001$; Fig. 2).

Given the trend toward significance for multivisceral resection and the divergent nature of the RFS curves for KIT mutation status in each of the categories of primary GIST and recurrent/metastatic GIST, we examined the impact of these variables on RFS for the *entire* patient population regardless of type of disease presentation (primary or recurrent/metastatic). Importantly, we found that stratifying patients into groups, exon 11, wild-type, and other (exons 9, 13, 17) revealed three distinct patterns of RFS, with patients whose tumors had exons 9, 13, or 17 mutations having the highest risk for recurrence ($p = 0.03$; Fig. 3). Additionally, use of multivisceral resection was also associated with higher risk of recurrence ($p = 0.011$; Fig. 3).

DISCUSSION

While the role of adjuvant TKIs for patients with high-risk GIST has been well delineated, application in the neoadjuvant setting has been less well studied. Previous studies demonstrated the safety of neoadjuvant treatment in regards to surgical morbidity.^{6,12,14,15} Our goal was to determine whether tumor or treatment characteristics can serve as prognostic factors to guide management of these complex patients by examining a consecutively treated cohort of patients with primary and recurrent/metastatic GIST. We

found that patients with recurrent/metastatic disease were more likely to require multiple TKIs and/or dose escalation during neoadjuvant treatment. Moreover, duration of therapy was significantly longer and disease progression was significantly higher in these patients. Despite these differences, the need for multivisceral resection at the time of surgery and incidence of margin-positive resections was similar between groups. We also determined that an extended period of neoadjuvant treatment predicted an increased risk of recurrence in patients with primary GIST. Moreover, analysis of the entire cohort of patients (both primary and recurrent/metastatic disease) demonstrated that KIT mutation status and need for multivisceral resection negatively impacted disease recurrence. Lastly, progression during neoadjuvant therapy was predictive of reduced OS in patients with recurrent/metastatic GIST.

Not surprisingly, the results of our study demonstrate that neoadjuvant treatment of primary GIST and recurrent/metastatic GIST are distinct entities. For primary disease, duration of therapy is a critical factor in disease recurrence. A previous study from our institution demonstrated that exceeding 10 months of therapy resulted in a significant increase in the number of patients who progressed on therapy.⁹ In the current study, the median duration of neoadjuvant therapy for primary GIST was 315 days (range 3–1,611), and there was a significant difference in RFS for patients treated for ≥ 365 days. The reasons for the wide range of neoadjuvant therapy duration included participation in treatment protocols with defined short-term neoadjuvant therapy, variable timing of referral from other centers, and impact of patient preference on timing of surgery. It was not possible to determine optimal treatment duration in this study; however, the negative impact of prolonged therapy was evident and is consistent with previously published reports suggesting that neoadjuvant therapy should not exceed 10–12 months. Understanding the mechanism behind this phenomenon will require further study but could be due to development of chemoresistance or new mutations secondary to prolonged therapy.

For metastatic/recurrent GIST, duration of neoadjuvant therapy [537 (range 4–3,257) days], was not a factor in oncologic outcomes. On the other hand, identification of tumor progression during neoadjuvant therapy was the only factor influencing OS. Disease progression was the primary reason for differences in neoadjuvant therapies among our patient cohorts. Understanding the reason for progression is more challenging. Patients who recurred during, or after, adjuvant TKI therapy may be at greater risk for developing GISTs with inherent TKI-resistance. In the event of multiple metastatic tumors, lesions may respond differently requiring a change in therapeutic strategy. Regardless of mechanism, disease progression during neoadjuvant therapy identifies patients at risk for mortality. Response to treatment could be employed to help guide the use of surgical resection for metastatic GIST.

In addition to the impact of duration of neoadjuvant therapy for primary GIST and the significance of disease progression during neoadjuvant treatment for recurrent/metastatic disease, we found that KIT mutation status may play a role in predicting risk of recurrence. Studies have demonstrated that exon 11 mutations tend to indicate imatinib sensitive disease and exon 9 mutations are less responsive, may require higher doses of imatinib and have a higher risk of recurrence.^{16–19} In our study, exons 9, 13, or 17 mutations were associated

with a higher risk of recurrence, although did not impact OS. Interestingly, in patients with wild-type GIST treated with neoadjuvant TKIs, there was improved RFS compared with patients harboring exon 11 mutations, which is contrary to published reports of higher risk of recurrence for patients without detectable KIT mutations.^{19,20}

This data must be interpreted with caution, because only patients who underwent surgical resection after therapy were included. Any patients who progressed, preventing surgical resection, were not captured. Furthermore, secondary to the small number of patients, the role of KIT mutation and its significance was identified through evaluation of *both* primary and recurrent/metastatic disease. Using our selection criteria, the primary GIST patient population is enriched for high-risk primary tumors secondary to location, perceived multivisceral involvement, and size, whereas for patients with recurrent/metastatic disease, the opposite is true and patients included in this study by definition were more likely to be resectable. While others have not demonstrated a predictive role for KIT mutations for disease recurrence, tumor exposure to therapy before resection may make KIT mutation status more significant for risk stratification. Future studies will need to include an assessment of impact of neoadjuvant TKIs on KIT mutations.

In conclusion, treatment of both primary and recurrent/metastatic GIST continues to evolve. The use of neoadjuvant TKI therapy, while complex potentially requiring dose adjustments and conversion to alternate TKIs, can be a valuable tool to help reduce tumor burden, predict disease biology, and perhaps help to define a role for surgical resection in the metastatic setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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FIG. 1. Kaplan–Meier survival curves depicting recurrence-free survival (a) and overall survival (b) stratified by primary and metastatic/recurrent gastrointestinal stromal tumors

FIG. 2.

Univariate analysis for prognostic factors for primary and metastatic/recurrent GIST demonstrates the significant impact of duration of neoadjuvant therapy on RFS for primary GIST. Importantly, the influence of progression of disease during neoadjuvant therapy on overall survival for patients with recurrent/metastatic GIST is also shown. There were trends toward significance seen for multivisceral resection predicting RFS in primary GIST and as well as disease progression on neoadjuvant TKI predicting RFS in recurrent/metastatic GIST

FIG. 3.

Univariate analysis of prognostic factors for all patients (primary and recurrent/metastatic) demonstrated the significant impact of multivisceral resection (a), and KIT mutation status (b) on recurrence-free survival (Kaplan–Meier curves)

TABLE 1

Patient and tumor characteristics

	Primary (<i>n</i> = 41)	Recurrent/ metastatic (<i>n</i> = 53)	<i>p</i> value
Median age (range)	62.5 (28–88)	59 (36–75)	0.2
Male gender, <i>n</i> (%)	26 (63.4)	36 (67.9)	0.7
Median tumor size at presentation, cm (range)	8.4 (2.9–21)	8.2 (0.8–31)	0.4
Median pathologic tumor size, cm (range)	6.5 (2–24)	6.5 (1–20.4)	0.7
Anatomic location (primary), <i>n</i> (%)			0.001
Gastric	27 (65.9)	16 (30.8)	
Small bowel	2 (4.9)	20 (38.5)	
Duodenum	5 (12.2)	9 (17.3)	
Rectum	5 (12.2)	4 (7.7)	
Other ^a	2 (4.9)	3 (5.8)	
KIT mutations, <i>n</i> (%)			0.6
Exon 11	26 (76.5)	28 (68.3)	
Wild-type	5 (14.7)	6 (14.6)	
Exons 9, 13, or 17	3 (8.8)	7 (17.1)	

^a Other locations include colon, esophagus, mesentery, and unknown

TABLE 2

Details of neoadjuvant TKI therapy and surgical resection

	Primary (<i>n</i> = 41)	Recurrent/ metastatic (<i>n</i> = 53)	<i>p</i> value
Number of neoadjuvant TKIs, <i>n</i> (%)			<0.0001
1	41 (100.0)	32 (61.5)	
>1	0 (0.0)	20 (38.5)	
TKI dose escalation, <i>n</i> (%)	0 (0.0)	22 (42.3)	<0.0001
Progression on TKI, <i>n</i> (%)	1 (2.4)	30 (58.8)	<0.0001
Median days of neoadjuvant TKI (range)	315 (3–1,611)	537 (4–3,257)	0.001
Multivisceral resection, <i>n</i> (%)	14 (34.1)	24 (46.2)	0.3
Margin positive resection, <i>n</i> (%)	2 (4.9)	4 (7.7)	0.6