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Adjuvant and Neoadjuvant Imatinib Therapy: Current Role in the Management of GIST

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Abstract

Although surgery remains the mainstay for the treatment of primary gastrointestinal stromal tumors (GIST), a significant number of patients experience disease recurrence within 5 years of surgery. The emergence of imatinib therapy for the treatment of patients with advanced GIST has offered unprecedented improvements in clinical outcomes for these patients. Prospective clinical trials have supported the efficacy and safety of imatinib prior to and following surgical resection of GIST. The American College of Surgeons Oncology Group Z9001 pivotal trial revealed that 1 year of adjuvant imatinib therapy provides significantly superior recurrence-free survival in patients with GIST following surgical resection, when compared with placebo. Additional trials and case studies have also begun to define the potential clinical benefit of imatinib in the neoadjuvant setting. Optimized risk stratification paradigms will be required to ensure the appropriate selection of patients to undergo treatment with imatinib in these settings. Risk stratification schemes are evolving that potentially will include mutation status and tumor rupture, and predictive nomograms have recently been proposed. The recent European Society of Medical Oncology and National Comprehensive Cancer Network guidelines mention use of adjuvant imatinib for 1 year in patients with KIT⁺, resectable GIST at high risk of recurrence. Moreover, the guidelines support the use of neoadjuvant imatinib in cases of limited disease if it would facilitate less extensive surgery and organ sparing. This article reviews pivotal efficacy and safety data for adjuvant imatinib and explores the potential clinical benefit of neoadjuvant imatinib in patients with GIST.

Keywords

Adjuvant; neoadjuvant; GIST; imatinib; tyrosine kinase inhibitor

Introduction

Gastrointestinal stromal tumors (GIST) are the most common tumor of the gastrointestinal (GI) tract.¹ GIST diagnoses have increased 25-fold over the past two decades, in part

because most smooth muscle tumors of the GI tract have been reclassified as GIST.¹ In an analysis of the US National Institutes of Health (NIH) Surveillance, Epidemiology, and End Results (SEER) patient registry, age-adjusted incidence of GIST diagnoses was shown to increase from 0.028 per 100,000 in 1992 to 0.688 in 2002.¹ Although mostly a result of reclassification, these figures represent a 50% increase in population- and age-adjusted GI mesenchymal tumor diagnoses. In 1992 and 2002, GIST comprised 6% and 82% of age-adjusted incidence of gastrointestinal mesenchymal tumors, respectively.¹ These results are comparable to other studies that report an incidence of 7 to 14 GIST cases per 1 million in the general population.^{2–8}

A seminal discovery was provided by Hirota and colleagues who demonstrated that stem-cell factor receptor (*KIT*) proto-oncogene *KIT* gain-of-function mutations caused GIST.⁹ This discovery arose from a hypothesis based on the observations that the interstitial cells of Cajal (ICC) express KIT, and mice homozygous for double mutants of *KIT* have disturbed GI movement. Based on these results, Hirota and colleagues hypothesized that gain-of-function mutations of *KIT* might induce neoplasms of ICC, which may present as mesenchymal tumors of the GI tract. GIST were regarded as a candidate for such neoplasms, and upon investigation, it was found that GIST do indeed express KIT-harboring gain-of-function mutations. In 2003, Heinrich and colleagues and Hirota's group both reported independently that gain-of-function mutations in platelet-derived growth factor receptor- α (*PDGFRA*) could be found in KIT-negative GIST.^{10,11} Approximately 80% of GIST contain an activating mutation in the *KIT* proto-oncogene, and 5% to 8% have activating mutations in *PDGFRA*.¹² *KIT* and *PDGFRA* mutations appear to be mutually exclusive oncogenic mechanisms in GIST.^{10,11}

Standard treatment for localized GIST is complete surgical resection (R0) with histologically negative margins.^{13,14} Median survival times underscore the importance of complete resection: median survival in patients with primary disease has been shown to be 66 months for complete resection and 22 months for incomplete resection.¹⁵ DeMatteo *et al.* reported a disease-free survival rate of 80% and 67% within years 1 and 2 after surgery, respectively; however, almost half of the patients experienced recurrence within 5 years. Collectively, these data emphasize the limited long-term benefit from surgical intervention alone.¹⁵

The introduction of imatinib mesylate (Glivec®/Gleevec® Novartis Pharmaceuticals, Basel, Switzerland), dramatically changed the treatment outlook for patients with GIST. Prior to the approval of imatinib, no systemic treatments had shown clinically meaningful improvements in outcomes for patients with advanced or metastatic GIST. In addition to the high rates of postoperative recurrence, available chemotherapeutic regimens failed to provide clinically relevant improvements in overall survival (OS). For example, in a study of patients with metastatic GIST who were treated with temozolomide (n=19), no complete response (CR) or partial response (PR), according to World Health Organization criteria, were observed, and the median time to disease progression was only 2.3 months.¹⁶ These data stand in contrast to response rates observed in a Phase III trial conducted by Verweij *et al.* in patients taking imatinib 400 mg/d (24/473, CR; 213/473, PR).¹⁷ In this latter study, OS estimates were 86% after 1 year and 69% after 2 years.¹⁷ Similar prospective trials have also demonstrated that

imatinib provides clinically significant benefit to patients with advanced GIST. For example, results from a large open-label trial of patients with metastasized or unresectable GIST treated with imatinib 400 mg/d showed a median time to progression of 24 months and a median OS of 55 months.¹⁸

The approval of imatinib, based on favorable efficacy and safety data in patients with unresectable, KIT+ metastatic/advanced GIST, has spurred a major transformation in the management paradigm for these patients. Its use recently has been extended to the adjuvant setting, and it has been evaluated in the preoperative (neoadjuvant) setting. Imatinib has been used after surgery to combat micrometastases that can lead to disease recurrence and death. Rigorous examination in a prospective trial has validated the clinical benefit of adjuvant imatinib given for 1 year after resection in patients with KIT+ GIST.¹⁹ These results served as the basis for which imatinib was approved for use in the United States and European countries for adult patients following resection of KIT+ GIST.²⁰ The approved uses are similar for patients in the United States and Europe, with the indication for the latter region carrying the qualifier that patients be at significant risk for relapse.^{21,22}

Less well studied is the role of neoadjuvant imatinib in GIST. Emerging data suggest that preoperative imatinib use may accomplish the dual task of treating distant micrometastases while treating the primary tumor without delay due to surgical planning. Additional data suggest that neoadjuvant therapy may reduce surgical morbidity by shrinking tumor volume, thereby improving the chances of complete resection. This article reviews the data on the use of imatinib in the adjuvant setting and explores emerging issues related to neoadjuvant use.

Prognostic Factors Following Surgery in GIST

Surgical removal remains the cornerstone of primary GIST treatment and complete surgical resection offers prognostic value toward risk of relapse.^{23–26} Nevertheless, resection is not the sole predictor of relapse risk or survival. Tumor size, location, and mitotic activity have all been studied to determine optimal diagnostic criteria, standardize disease severity grades, and better understand prognostic factors. Emory *et al.* noted, however, that while tumor size, location, and mitotic index offer predictive value, none of these factors alone sufficiently predicts clinical course.^{27,28} In 2001, the NIH assembled a consensus panel to standardize diagnostic and prognostic practices in GIST.²⁸ From the 2001 NIH consensus panel, the first widely accepted risk stratification scheme (NIH consensus criteria) was developed that shifted away from the binary classification of malignant versus benign to one assigning risk for aggressive course based on tumor size and mitotic index.²⁸ In addition to size and mitotic activity, some investigators have advocated that tumor location and rupture status at resection be included in the NIH stratification scheme,²⁹ because these factors also have been shown to affect prognosis.²⁶

Since the publication of the consensus panel guidelines, knowledge about the prognostic importance of *KIT* mutations in GIST has increased exponentially. Although tumor size, mitotic index, and location remain proven prognostic indicators, information related to mutational status is increasingly informing prognostics and treatment regimens. Recently, data from the American College of Surgeons Oncology Group (ACOSOG) Z9001 trial

confirmed standard prognostic criteria and validated the use of molecular features. A multivariate analysis of their results showed that mitotic rate ($P<0.0001$; hazard ratio [HR], 17.07), tumor size ($P<0.0026$; HR, 1.70), small bowel location (vs gastric location; $P<0.0267$; HR, 2.08), and *KIT* exon 11 mutations (vs wild type; $P=0.042$; HR, 2.97) independently predicted recurrence risk in patients in the placebo arm.³⁰

As an alternative to risk stratification schemes that categorize risk of recurrence into discrete groups, Gold *et al.* have reported on a nomogram that quantitatively predicts recurrence-free survival (RFS) on a continuous scale, according to assigned points based on tumor size, location, and mitotic index.³¹ In contrast to the Gold nomogram, which predicts RFS in patients with resected primary GIST, Goldstein *et al.* have developed a nomogram that predicts OS at 5 years in patients with locally advanced or metastatic GIST.³² The following pretreatment variables were included in the nomogram, and all independently predicted shorter survival time: metastatic disease (as opposed to locally advanced disease), high mitotic rate, high neutrophil count, and absence of *KIT* exon 11 mutations.

Role of Adjuvant Therapy in GIST

With the approval of imatinib for advanced GIST came studies that suggested improved clinical benefit and safety for patients with primary GIST (Table 1). Individual case studies, retrospective analyses, and a non-randomized study first reported the potential recurrence-free benefits and safety of imatinib in the adjuvant setting.^{33–36} The ACOSOG Z9000 study first established the efficacy of imatinib for 1 year of adjuvant therapy in patients with resected GIST.³⁷ This single-arm, open-label, multicenter, Phase II trial enrolled 107 patients with resected (R0) *KIT*⁺ GIST at high risk for disease recurrence.³⁷ Recurrence risk factors included large primary tumor size ≥ 10 cm, tumor rupture, or <5 peritoneal metastases. After a median follow-up of 4 years, OS rates were 99% (year 1), 97% (year 2), and 97% (year 3). The RFS rates were 94%, 73%, and 61% for the first, second, and third years, respectively. By comparison with another study, DeMatteo *et al.* demonstrated that 54% of patients with primary GIST treated with resection alone (R0) experienced disease recurrence within 5 years of surgery.¹⁵

Results from the pivotal Phase III, double-blind ACOSOG Z9001 trial prompted the approval of imatinib for the adjuvant treatment of patients following resection of *KIT*⁺ GIST.¹⁹ In this study, all enrolled patients (N=713) underwent complete surgical resection of primary *KIT*⁺ GIST (≥ 3 cm) and were randomized to receive imatinib 400 mg/d or placebo for 1 year. Although designed as a double-blind trial, patients were permitted to cross over to the imatinib arm upon disease recurrence. During the treatment period, 41 patients discontinued in the placebo arm due to disease recurrence, and 11 discontinued because of adverse events. One patient on imatinib discontinued treatment due to disease recurrence, while 57 patients discontinued because of adverse events.¹⁹

The Z9001 trial results showed significantly prolonged 1-year RFS in patients receiving imatinib versus placebo (98% vs 83%; HR, 0.35 [95% confidence interval (CI) 0.22–0.53]; $P<0.0001$; Figure 1).¹⁹ A subgroup analysis revealed that patients with the largest tumors (≥ 10 cm) derived the most clinical benefit.¹⁹ As mentioned, these results served as the basis

on which imatinib was approved for use in the United States and in European countries for adult patients following resection of KIT^+ GIST. The approved uses are similar for patients in the United States and Europe, with the indication for the latter region carrying the qualifier that patients be at significant risk for relapse.^{21,22}

A limitation of the ACOSOG Z9001 trial is its relatively short median follow-up time (19.7 months).¹⁹ Once interim-analysis–demonstrated efficacy criteria had been achieved, the trial was stopped, and preliminary results were published before completion. Thus, the median follow-up duration of patients falls short of the median time to progression of 24 months observed for patients with metastatic GIST on imatinib therapy.¹⁸ As seen in Figure 1A, approximately 6 months after stopping adjuvant imatinib, the recurrence rate increased sharply for patients in the treatment arm and began to approach the curve of the placebo group. Moreover, differences in OS were not statistically significant (Figure 1B; $P=0.47$; HR, 0.66 [95% CI 0.22–2.03]), which, in addition to insufficient follow-up, may have been due to the trial design allowing for patient crossover to treatment upon recurrence.¹⁹ Longer follow-up is needed to determine the long-term benefits if any for 1 year of adjuvant imatinib therapy.

Further evaluation of the impact of tumor pathologic and molecular factors on outcomes in a subpopulation of patients from the Z9001 trial have been recently reported.³⁰ After 1 year of imatinib therapy, the 2-year RFS (i.e. 1 year after stopping therapy) rate was 91% for imatinib-treated patients with KIT exon 11 mutations versus 65% for patients with this genotype on placebo (control; $P<0.0001$).³⁰ These findings are consistent with other studies that have shown that patients with KIT exon 11 mutations respond well to adjuvant imatinib therapy.^{36,38,39} Over the same time period, relapse-free rates for imatinib-treated patients with GIST expressing $PDGFR\alpha$ mutations were 100% ($n=29$) versus 71% ($n=28$) for the control arm ($P<0.01$ at 24 months).³⁰ Patients with D842V $PDGFR\alpha$ mutant-GIST, a genotype with demonstrated *in vitro* and clinical resistance to imatinib, were represented in both arms (100% 2-year RFS, $n=15$ imatinib; 90% 2-year RFS, $n=13$ control).^{40–42} Patients taking imatinib who had GIST with mutations in KIT exon 9 showed an improved 1-year RFS rate while on drug (100% imatinib [$n=13$] vs 20% control [$n=22$]), but no improvement as assessed by 2-year RFS rate was observed between treatment arms once imatinib treatment was discontinued.³⁰ Although no statistical differences were observed between these small, unbalanced treatment arms, these results suggest that imatinib 400 mg may delay recurrence in patients with KIT exon 9 mutations. Lastly, patients with wild-type KIT tumors showed no statistically significant difference in response to imatinib or control.³⁰ Collectively, these results suggest that GIST mutation status has predictive value in regard to response to adjuvant imatinib.

The incidence of disease recurrence after imatinib discontinuation in ACOSOG Z9001 has prompted additional trials that evaluate longer (>1 year) durations of adjuvant imatinib therapy. Recent investigations from the Peking University School of Oncology analyzed data from 105 non-randomized patients with resected GIST at high risk of recurrence.⁴³ Patients received imatinib (400 mg/d) or no treatment with a follow-up period of 12 to 36 months (median 20 months). Treatment with imatinib produced a significantly longer RFS compared with no treatment at 1-, 2-, and 3-years (100% vs 90%, 96% vs 57%, 89% vs 48%,

respectively; $P < 0.0001$; HR=0.188; 95% CI 0.085–0.417), respectively.⁴³ In contrast to the ACOSOG Z9001 trial, overall survival was significantly higher for imatinib-treated patients compared with no treatment ($P=0.025$), as adjuvant imatinib significantly reduced the risk of death (HR=0.254; 95% CI 0.070–0.931).⁴³

In a Phase II study conducted by Kang *et al.*, 47 patients with moderately sized, curatively resected high-risk localized GIST (R0, mean size 7.5 cm) with *KIT* exon 11 mutations received adjuvant imatinib (400 mg/d) for 2 years or until recurrence or discontinuation (median follow-up 26.9 months).³⁸ Results from this study supported the clinical benefit of adjuvant imatinib in patients with high-risk GIST with 1-year and 2-year RFS rates of 97.7% and 92.7%, respectively.³⁸

In a randomized, Phase II trial of 19 patients with primary or limited metastatic GIST, McAuliffe *et al.* were the first to combine a brief neoadjuvant course (300 mg bid for 3, 5, or 7 days) with 2 years of adjuvant imatinib therapy (600 mg/d).⁴⁴ The median disease-free survival was 46 months (range 10–46 months, median follow-up 32 months) in this study. All patients whose tumor recurred within the 2-year adjuvant interval had discontinued imatinib due to toxicity or transportation problems getting to the treatment center. Disease recurrence was reported in 6 patients after the 2-year completion time. In these patients, median time to disease progression was 4 months after imatinib discontinuation. This was the first prospective, randomized trial to show the safety and efficacy of neoadjuvant and adjuvant imatinib, with criteria of response by imaging and by apoptotic index.⁴⁴ Importantly, these data also demonstrated reductions in glucose metabolism and cell death at the tumor site within the first week of neoadjuvant imatinib.⁴⁴ Interestingly, the rate of apoptosis increased in direct relation to the duration of neoadjuvant imatinib therapy, although the duration of neoadjuvant therapy did not impact disease-free survival rates.⁴⁴

Prospective, randomized clinical trials are assessing the clinical benefit and tolerability of adjuvant imatinib >1 year and promise to provide invaluable insights into the proper duration of therapy. The European Organisation for Research and Treatment of Cancer (EORTC) is conducting a Phase III, randomized clinical trial to compare adjuvant imatinib for 2 years to observation (no treatment) in patients with completely resected, localized, intermediate-or high-risk GIST.⁴⁵ The Phase III Scandinavian Sarcoma Group (SSGXVIII/AIO) trial is comparing 1 year with 3 years of adjuvant imatinib (400 mg/d) therapy in patients with high-risk GIST.⁴⁶ Lastly, the Post-resection Evaluation of Recurrence-free Survival for GastroIntestinal Stromal Tumors with adjuvant imatinib (PERSIST-5) Phase II, non-randomized, open-label, multi-centre, study will evaluate RFS following the complete resection of significant risk primary GIST in patients treated with adjuvant imatinib (400 mg/d) for 5 years.⁴⁷

Neoadjuvant imatinib: An Evolving Paradigm

Results from case studies and retrospective analyses have prompted further investigation into the use of imatinib as a neoadjuvant therapy (Table 2).^{48–50} In this setting, imatinib is administered to patients weeks, months, or even years prior to surgical resection.^{51–54}

Andtbacka *et al.* performed one such study in 46 patients who underwent surgical resection following imatinib treatment.⁵¹ In this study, patients were divided into two groups: 35 patients (76%) had locally advanced primary GIST, and 11 patients (24%) had recurrent or metastatic GIST.⁵¹ Patients in both groups were treated with imatinib (400 mg/d) for a median of 12.9 months prior to surgery.⁵¹ Radiographic assessment of tumor size prior to surgery showed 82% of patients in the locally advanced primary GIST subgroup had a CR or PR to imatinib therapy with a corresponding 85% median decrease in tumor volume.⁵¹ In this group, all 11 patients (100%) achieved complete surgical resection and were found to be disease free at a median follow-up of 19.5 months post surgery.⁵¹ In patients with recurrent or metastatic GIST, 31% achieved complete resection, whereas 69% had incomplete resection.⁵¹ A determining factor for whether patients achieved complete resection was response to and duration of imatinib therapy.⁴⁸ Moreover, patients achieving complete resection had a significantly shorter regimen of preoperative imatinib than those achieving partial resection.⁵¹

Similar studies have also shown benefits of neoadjuvant imatinib treatment.^{55,56} Goh *et al.* investigated the effects of imatinib on surgical treatment, positron-emission tomography scan response, and outcome after surgical resection in 37 patients with GIST.⁵⁵ The results of this case report (n=1) combined with a literature review (n=36) showed that 89% of patients with GIST included in this analysis were able to achieve complete resection following neoadjuvant imatinib treatment, with 74% of patients being disease free at a median of 6 months follow-up.⁵⁵ Hohenberger *et al.* examined the effects of imatinib on extent of surgery, morbidity, and response to therapy in 36 patients with locally advanced GIST (median tumor size: 10.5 cm).⁵⁶ For the 33 patients (92%) who completed 6 months of preoperative imatinib, median tumor size was reduced to 5.5 cm. Furthermore, 28 of the 31 (90%) patients who completed 6 months of neoadjuvant imatinib had complete tumor removal, although 2 patients showed previously undetected peritoneal spread (R2). Moreover, 5 of the 6 patients that were previously considered inoperable underwent surgery after neoadjuvant treatment. Lastly, more conservative surgeries than initially planned could be implemented in 21 of the 25 remaining patients.⁵⁶ In all, these studies provide compelling evidence that neoadjuvant imatinib enables patients with formerly inoperable GIST to achieve complete resection and potentially better clinical outcomes.

The successful application of imatinib in the neoadjuvant setting has set the stage for the development of several clinical trials designed to further assess the benefit and safety of neoadjuvant therapy. The results of one Phase II⁴⁹ and one Phase III⁵⁷ clinical trial have been published, and a third Phase II trial has been completed with results pending (Table 2).⁵⁵

The Phase II Radiation Therapy Oncology Group/American College of Radiology Imaging Network (RTOG 0132/ACRIN 6665) study was conducted to evaluate the efficacy and safety of neoadjuvant imatinib (600 mg/d) for patients with primary or operable metastatic GIST.⁴⁵ This two-arm trial comprised 52 analyzable patients (63 total) who were treated with imatinib for 8 to 12 weeks prior to surgery (median time 65 days): group A patients had primary GIST (58%), and group B patients had metastatic/recurrent GIST (42%).⁴⁹ Overall, imatinib was well tolerated, with a favorable toxicity profile, and the majority of patients

completed the treatment course prior to surgery.⁴⁹ The preoperative Response Evaluation Criteria in Stromal Tumors (RECIST) responses in group A were: 2 PR (7%), 25 stable disease (SD; 83%), and 3 unknown (10%); group B RECIST responses were: 1 PR (4.5%), 20 SD (91%), and 1 progressive disease (4.5%). Complete resection, defined as removal of all gross and microscopic disease, was achieved in 77% of patients in group A and 58% of patients in group B.⁴⁹ Patients in group A also showed a 2-year estimated progression-free survival (PFS) of 83% and an OS of 93%.⁴⁹ The majority of the surgeries performed in this trial preserved organs and their function, perhaps due in part to reduction in tumor size facilitated by neoadjuvant imatinib therapy. In addition, it is possible that neoadjuvant imatinib therapy may have prevented seeding of tumor cells and bleeding during resection, although the results of this trial did not confirm these hypotheses.⁴⁹

In a retrospective sub-analysis of the BFR14 Phase III trial, Cassier *et al.* evaluated the benefits of combining neoadjuvant imatinib and surgical resection in patients with locally advanced GIST.⁵⁹ In this analysis, patients with recurrent disease or metastases were excluded from analysis.⁵⁹ Nine of the 25 assessed patients underwent complete resection following a median of 7.3 months of imatinib treatment.⁵⁹ All patients who underwent surgical resection showed significantly longer PFS compared with those who did not (not reached vs 23.6 months, $P=0.0322$).⁵⁹

A second Phase II trial has recently been completed. The CST1571-BDE43 trial (i.e. Apollon) led by researchers at Technische Universität München is a nonrandomized, open-label, multicenter trial designed to examine the tumor response to imatinib when administered as a preoperative therapy.⁵⁸ Patients in this study were given imatinib twice daily for 4 to 6 months, and those who showed a response to imatinib treatment or had SD (no progression) underwent surgery for complete resection.⁵⁵ The results of this study are yet to be published, but are highly anticipated.

ESMO and NCCN Guidelines for Adjuvant and Neoadjuvant Therapy

Although the European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines both mention adjuvant imatinib therapy be considered as a treatment option for patients at risk of recurrence, the two differ in their support for such therapy, with the ESMO guidelines stance being more conservative.^{13,60} The NCCN guidelines recommend ‘adjuvant imatinib or observation for patients who are at *significant* risk of recurrence after undergoing complete resection’. According to ESMO guidelines, there is no global consensus on the use of imatinib as adjuvant therapy for localized GIST, although it may be used for 1 year as adjuvant therapy in patients at *high risk* of relapse. In addition, although the ESMO guidelines mention the preliminary ACOSOG Z9001 data, they highlight the finding that, currently, there are no overall survival data for imatinib. Moreover, based on the short follow-up of patients on ACOSOG Z9001, the ESMO guidelines also state that, ‘a longer follow-up is needed to draw definitive conclusions with regard to: the absolute relapse rate after a substantial time interval, the length of the delay in relapse, and the time to secondary resistance to imatinib.’

ESMO currently recommends preoperative imatinib as an option for patients with limited disease, if it results in less mutilating surgery and lower risk of tumor bleeding and rupture (Table 3).¹⁴ Moreover, for patients with extensive disease, the ESMO guidelines state that, while conclusive results are under investigation, enrollment of patients in ongoing clinical trials studying the effects of complete excision following imatinib treatment is encouraged.¹⁴ Similarly, the NCCN guidelines state that for multivisceral resection in primary GIST, a preoperative imatinib regimen may be beneficial.¹⁴ They also state that metastatic GIST may be operable following successful response to imatinib treatment.¹³

Conclusions

The diagnosis and treatment of patients with GIST is rapidly evolving as the knowledge based on the pathobiology of these tumors and the optimal use of available therapeutic agents in the preoperative and postoperative settings continues to accumulate. Although the M-L/AFIP risk stratification scheme remains the most widely used, the past decade of GIST research has identified new prognostic factors and developed paradigms that may result in more precise risk stratification schemes, especially in the adjuvant setting. Moreover, the pivotal ACOSOG Z9001 trial along with others studies, has demonstrated the unequivocal clinical benefit of adjuvant imatinib in patients with KIT⁺ GIST. However, the effects of adjuvant imatinib therapy on OS and the optimal duration of therapy remain the subject of ongoing research. Data from case reports and small clinical trials suggest that neoadjuvant imatinib therapy can improve the likelihood of achieving complete resection and enhance patient clinical outcomes. Nevertheless, more data are needed from prospective, randomized clinical trials before a definitive clinical benefit can be determined. After a decade, imatinib remains the first-line treatment of patients with metastatic GIST, and new therapeutic applications that may improve outcomes of patients with primary GIST warrant clinical consideration.

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Abbreviations used:

ACOSOG	American College of Surgeons Oncology Group
AFIP	Armed Forces Institute of Pathology
AIG	Arbeitsgemeinschaft Interistisch Onkologie
C	control
CI	confidence interval
CR	complete response
CT	computed tomography
ESMO	European Society of Medical Oncology

EORTC	European Organisation for Research and Treatment of Cancer
GIST	gastrointestinal stromal tumors
HPF	high-powered fields
HR	hazard ratio
ICC	interstitial cells of Cajal
KIT	stem cell factor
M-L/AFIP	Miettinen-Lasota/Armed Forces Institute of Pathology
MFU	median follow-up
NCCN	National Comprehensive Cancer Network
NIH	National Institutes of Health
OS	overall survival
PDGFRA	platelet-derived growth factor receptor- α
PERSIST-5	Post-resection Evaluation of Recurrence-free Survival for GastroIntestinal Stromal Tumors with adjuvant imatinib
PFS	progression-free survival
PR	partial response
RCT	randomized, controlled trial
RECIST	Response Evaluation Criteria in Stromal Tumors
RFS	relapse-free survival
RTOG 0132/ACRIN 6665	Radiation Therapy Oncology Group/American College of Radiology Imaging Network study
SD	stable disease
SEER	Surveillance, Epidemiology, and End Results
SSGXVIII/AIO	Phase III Scandinavian Sarcoma Group trial
TKI	tyrosine kinase inhibitor

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Novelty and Impact Statement

Gastrointestinal stromal tumors (GIST) represent a unique tumor type wherein the receptor tyrosine kinases KIT, and to a lesser extent platelet-derived growth factor receptor alpha (PDGFR- α), underlie their aberrant behavior. The introduction of the tyrosine kinase inhibitor imatinib mesylate, an inhibitor of KIT and PDGFR- α , has significantly changed the way GIST is managed, affording patients prolonged survival in the advanced stages of disease. Although surgical resection remains the mainstay for the treatment of primary GIST, the majority of resectable patients experience disease recurrence, and some patients can present with unresectable disease. Recently completed clinical trials using imatinib in the adjuvant and neoadjuvant settings have shed light on the potential use of this agent in these respective settings. The American College of Surgeons Oncology Group Z9001 trial has demonstrated that 1 year of adjuvant imatinib therapy provides significantly superior median relapse-free survival in selected patients with GIST following complete surgical resection when compared with placebo. Moreover, prospective clinical trials, retrospective reviews and case studies have demonstrated the utility of imatinib in the neoadjuvant setting. Together, usage in these therapeutic settings has increased, and these are evolving issues in GIST patient management. Accruing data from ongoing trials in both of these settings will likely have a major impact on how patients with GIST will be managed. A descriptive review of the current data surrounding these topics would be an invaluable asset for clinicians and healthcare professionals involved in the management of this rare solid tumor.

Figure 1:

Recurrence-free survival (A) and overall survival (B) in the ACOSOG Z9001 trial¹⁹

Reprinted from *The Lancet*, 373, DeMatteo RP, Ballman KV, Antonescu CR, *et al.*, Adjuvant imatinib mesylate after resection of localized, primary gastrointestinal stromal tumour: a randomized double-blind, placebo-controlled trial, 1097–1104, Copyright (2009) with permission from Elsevier.

ACOSOG, American College of Surgeons Oncology Group; CI, confidence interval; HR, hazard ratio.

Table 1.

Key Adjuvant Clinical Trials in GIST

Trial (Phase)	Imatinib Dosage and Duration	Patients	OS	RFS	Safety
ACOSOG Z9000 2008 ³⁷ Phase II Single-arm, open-label, multicenter study	400 mg/d for 12 mo MFU: 4 years	N=107 Resected KIT ⁺ primary GIST (R0) with high recurrence risk	Yr 1: 99% Yr 2: 97% Yr 3: 97%	94% 73% 61%	Well tolerated
ACOSOG Z9001, 2009 ¹⁹ Phase III randomized, double – blind, placebo-controlled trial Patients with recurrence could cross over to imatinib treatment	400 mg/d for 12 mo MFU: 19.7 mos	N=713 Resected KIT ⁺ primary GIST (R0, 3 cm)	No difference between IM and C groups	Yr 1: 98% for IM vs 83% for C [*]	Gr 3/4 AEs occurred in 63 (18%) patients in C group and 104 (31%) in the IM group
Li <i>et al.</i> 2011 ⁴³ Single-center, nonrandomized, open contrast	400 mg/d 12 to 36 mos (median 20 mos) MFU: 45 mos	N=105 Resected GIST (R0) with medium-to-high recurrence risk	NA	Yr 1: 100% for IM vs 90 for C [*] Yr 2: 96% for IM vs 57% for C [†] Yr 3: 89% IM vs 48% C	The most common AEs in treated pts were (%): edema (Gr 1/2, 86%); fatigue (Gr 1/2, 21%, Gr 3/4, 2%); granulocytopenia (Gr 1/2, 34%; Gr 3/4, 5%; and rash (Gr 1/2, 27%; Gr 3/4, 4%)
Kang <i>et al.</i> 2009 ³⁸ Phase II, multicenter trial (4 Korean centers)	400 mg/d for 2 years until recurrence or discontinuation MFU: 26.9 mos	N=47 Resected GIST (R0) with <i>KIT</i> exon 11 mutations and high recurrence risk	NA	Yr 1: 97.7% Yr 2: 92.7%	The treatments were generally well tolerated Gr 3/4 toxicities included: neutropenia 27.7%, rash 8.5%, constipation 4.3%, anorexia 2.1%, vomiting 2.1%, and pruritus 2.1%
McAuliffe <i>et al.</i> ⁴⁴ Phase II, prospective, randomized trial	Neoadjuvant: 300 mg bid, for 3, 5, or 7d Adjuvant: 600 mg/d for 2 years MFU: 32 mos	N=19 Resected KIT ⁺ GIST (1 cm) preceded by neoadjuvant imatinib	NA	Yr 1: 94% Yr 2: 87% 100% in patients who completed the full 2 years of adjuvant therapy	5 Gr 4 AEs occurred in 4 (22%) patients: 2 perioperative vascular events, 1 non-Q-wave myocardial ischemia, 1 transient ischemic event, [†] 1 anemia
EORTC 62024 ⁴⁵ Phase III, prospective, RCT	0 vs 2 years	N=906 KIT ⁺ completely resected GIST with intermediate or high recurrence risk	Primary endpoint: TTSR	Data expected in 2011	Data expected in 2011
SSG XVII AIG ⁴⁶ Phase III, open-label, multicenter, prospective RCT	400 mg/d for 1 vs 3 years	N=400 Resected GIST (R0) with high risk of recurrence	Primary outcome: RFS	Data expected in 2011	Data expected in 2011
PERSIST-5 ⁴⁷ Phase II, open-label, multicenter, prospective RCT	400 mg/d for 5 years	N=133 (target) Resected GIST (R0) with significant risk for recurrence	Primary outcome: RFS	NA	NA

ACOSOG, American College of Surgeons Oncology Group; AE, adverse event; AIG, Arbeitsgemeinschaft Internistische Onkologie; C, control; EORTC, European Organisation for Research and Treatment of Cancer; Gr, Grade; IM, imatinib; MFU, median follow-up; NA, not available; OS, overall survival; RCT, randomized, controlled trial; RFS, recurrence-free survival; SSG, Scandinavian Sarcoma Group; TTSR, time to secondary resistance

* $P < .01$;

[†] patients had pre-existing vascular disease.

Table 2.**Key Neoadjuvant Clinical Trials in GIST**

Trial (Phase)	Imatinib Dosage and Duration	Patients	Outcomes	Safety
RTOG S032/ ACRIN 6665 ⁴⁹ Phase II, nonrandomized, prospective trial	Neoadjuvant: 600 mg/d for 8–12 wks Adjuvant: 400 mg/d for 2 yrs Follow-up: 3 yr	N=63 (52 analyzable): 30 with primary GIST; 22 with recurrent/metastatic	Primary GIST: 7% PR; 83% SD; 10% unknown Recurrent GIST: 4.5% PR; 91% SD; 4.5% PD 2-yr PFS: 83% for primary; 77% for recurrent 2-yr OS: 93% for primary; 91% for recurrent	Post-operative toxicities: 29% Gr 3; 16% Gr 4; 4% Gr 5
BFR14 substudy ⁵⁹ Phase III, BFR14 database sub-analysis (retrospective)	Median treatment duration prior to surgery: 7.3 mos	N=25 (9 patients underwent resection) locally advanced GIST without metastases	Median PFS: not reached for resected vs 29.4 mos for non-resected Median OS: Median not reached for resected vs 42.2 [*] months for non-resected	NA
Apollon CST1571 BDE43 Phase II, open label trial ⁵⁵	400 mg/d for 4–6 mos	N=40 (target)	Primary endpoint: overall tumor response	NA

DFS, disease-free survival; Gr, grade; NA, not available; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RFS, recurrence-free survival; SD, stable disease.

^{*} $P < 0.05$.

Table 3.

2010 ESMO/NCCN Guidelines

Guidelines	Adjuvant/Neoadjuvant Imatinib Treatment for Primary GIST
NCCN, 2010 ¹³	<p>Adjuvant:</p> <ul style="list-style-type: none"> • Adjuvant therapy for 12 months should be considered in patients with <i>intermediate to high risk</i> GIST (ACOSOG Z9001 trial mentioned) • The optimal duration has not yet been determined. Patients at significantly higher risk for disease recurrence may justify a longer course • Adjuvant IM should be continued if any persistent gross disease is seen following resection <p>Neoadjuvant:</p> <ul style="list-style-type: none"> • Recommended for patients with marginally resectable GIST, or for patients whose surgical morbidity could be improved by preoperative reduction of tumor size • Close monitoring is essential as some patients that are marginally resectable may rapidly progress to unresectable • PET may give indication of IM activity after 2 to 4 weeks of therapy, although PET is not a substitute for diagnostic CT • No distinction made between dosing for preoperative and other settings; recommended starting dose is 400 mg/day, but a dose of 800 mg/day should be considered for those patients with <i>KIT</i> exon 9 mutations • Dosing can be stopped right before surgery and restarted as soon as the patient is able to tolerate oral medications
ESMO, 2010 ¹⁴	<p>Adjuvant:</p> <ul style="list-style-type: none"> • Adjuvant IM can be proposed as an option for patients with a <i>substantial risk of relapse</i>, for shared decision making • Mutational analysis may help guide the selection of those patients who are more likely to benefit from adjuvant IM • Currently available trial data support the use of adjuvant IM for 1 year • Patients with tumor rupture at the time of surgery are at a very high risk of peritoneal relapse and should be considered for adjuvant IM therapy; the optimal duration of treatment is unknown <p>Neoadjuvant:</p> <ul style="list-style-type: none"> • If R0 surgery is not feasible, or if it could be achieved through less-mutilating surgery with cytoreduction (i.e. tumor size reduction), IM pretreatment is recommended; this is also the case if the surgeon believes the surgery could be made safer (i.e. decreased bleeding and tumor rupture) • Mutational analysis may help exclude non-sensitive mutations (e.g. <i>PDGFRA</i> D842V) from consideration for preoperative therapy • PET scan, or PET and CT/MRI, may be useful to assess tumor response rapidly in the case of non-responding disease

ACOSOG, American College of Surgeons Oncology Group; CT, computed tomography; ESMO, European Society for Medical Oncology; IM, imatinib; MRI, magnetic resonance imaging; NCCN, National Comprehensive Cancer Network; PET, positron-emission tomography.