Continuous imatinib therapy in patients with gastrointestinal stromal tumors

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Patients with gastrointestinal stromal tumors (GIST) used to have a poor prognosis due to the very low response rate of these tumors to conventional chemotherapy and radiation therapy. However, following the introduction of imatinib as a targeted therapeutic agent with efficacy in GIST, survival outcomes have improved remarkably for patients in the advanced/metastatic and adjuvant settings. Imatinib is now approved for both indications and has become the standard of care for patients with GIST. Despite the mounting evidence demonstrating the clinical benefits of extending imatinib treatment beyond 1 year, the optimal duration of imatinib therapy has not yet been determined. Similarly, whether *chronic* or *extended* adjuvant imatinib therapy can further improve clinical outcomes in patients with GIST remains to be determined. In this review, we present recent findings from various clinical trials which indicate that prolonged, uninterrupted imatinib treatment can have durable clinical benefits in patients who underwent resection of primary, operable GIST, as well as patients with advanced, unresectable, or metastatic GIST. We also summarize data showing that treatment interruption can result in disease progression in both the adjuvant and advanced/metastatic settings. Finally, we present evidence from different trials that long-term imatinib therapy is feasible and safe (ie, without cumulative toxicities) in patients with GIST.

Treatment of GIST using the oral tyrosine kinase inhibitor (TKI) imatinib has significantly improved survival outcomes in the advanced/metastatic and adjuvant settings.[1-4] The B2222 trial showed that nearly 50% of patients with advanced or metastatic GIST who were treated with imatinib survived over 5 years,[5] compared with 14-24 months for historical controls treated with traditional chemotherapy.[6,7] The ACOSOG Z9001 trial then showed that imatinib significantly improved recurrence-free survival (RFS) following resection of primary GIST, resulting in the adjuvant label for imatinib.[4] Additionally, the phase 3 SSGXVIII/AIO trial showed that 3 years of adjuvant imatinib therapy after complete resection of primary GIST further extended the 5-year RFS and overall survival (OS) rates from 47.9% to 65.6% ($P < .001$) and 81.7% to 92.0% ($P = .02$), respectively, compared with 1 year of therapy.[8] Based on these results, imatinib is currently approved as first-line treatment of KIT-positive, unresectable, advanced or metastatic GIST, as well as first-line adjuvant treatment after resection of KIT-positive GIST.[9]

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Although the optimal duration of treatment has not been determined, evidence suggests that continuation of imatinib therapy is important to delay disease progression and recurrence.[4,8,10-15] The National Comprehensive Cancer Network (NCCN) guidelines recommend continuous imatinib treatment until disease progression in the advanced/metastatic setting[16] and, more recently, both the product label and guidelines were updated to recommend at least 3 years of adjuvant imatinib therapy in patients at high risk of recurrence following resection of primary GIST.[9,16] We review here clinical data showing that continuous, uninterrupted imatinib treatment is beneficial for patients with GIST in both the advanced/metastatic and adjuvant settings.

Improved survival outcomes with longer imatinib treatment duration

Before the introduction of imatinib, median OS for patients with advanced or unresectable GIST treated with conventional cytotoxic chemotherapy and radiation therapy ranged from 14 to 24 months.[6,7] For patients with locally recurrent GIST, median OS was only 9 to 12 months.[17] Following the discovery that KIT gain-of-function mutations were present in 75%-80% of cases of GIST, and the hypothesis that, as a KIT inhibitor, imatinib might have therapeutic utility in GIST,[7] Demetri et al were the first to show

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clinical benefit from 1 year of imatinib treatment in 81.6% of patients with unresectable or metastatic GIST (53.7% had a partial response [PR]; 27.9% had stable disease [SD]).[1] In this B2222 trial, the estimated 1-year OS rate was 88% and median OS had not been reached at study end (68 weeks after patients received the first dose of imatinib),[1] suggesting an improvement over the historical survival time.[6,7]

Subsequently, extended treatment durations also demonstrated improved progression-free survival (PFS) and OS rates. Verweij et al conducted a longer trial (EORTC 62005) in which they followed 946 patients with advanced/unresectable GIST who were treated with imatinib for 2 years. The 2-year PFS and OS rates were 47% and 69%, respectively.[2] Similarly, in the Southwest Oncology Group S0033 trial, Blanke et al followed 147 patients with advanced/unresectable GIST who were treated with imatinib for 4.5 years.[3] Their results revealed a median PFS of 18 months, whereas median OS was extended to 55 months. Overall, these results thus suggest that longer durations of imatinib therapy can significantly improve survival in patients with unresectable, advanced, or metastatic GIST, compared with historical, untreated controls.

TABLE 1 Progression-free survival in patients with GIST who received imatinib for a longer duration in the advanced or metastatic setting

Treatment	Study	Duration of treatment, y	PFS		
			Follow-up, %		Median, mo
			1-year	2-Year	
Continued imatinib	Blay et al[10]	> 1	69	–	18
	Le Cesne et al[11]	> 3	92	80	NR
	Ray-Coquard et al[12]	> 5	100	–	–
Interrupted imatinib	Blay et al[10]	1	19	–	6
	Le Cesne et al[11]	3	32	15	9
	Ray-Coquard et al[12]	5	55	–	–

Abbreviations: GIST, gastrointestinal stromal tumors; NR, not reached; PFS, progression-free survival.

The clinical benefit of imatinib treatment has also been demonstrated in the adjuvant setting. Even though complete resection remains the only potentially curative treatment for GIST and many patients undergo surgical resection as their primary treatment, about 50% of them relapse within 5 years after surgery alone, emphasizing the need for adjuvant therapy.[17,18] In the ACOSOG Z9001 trial, DeMatteo et al followed 713 patients who received 1 year of imatinib or placebo treatment after resection of primary GIST.[4] Their results showed that the 1-year RFS rate was higher in the imatinib group (98%) than in the placebo group (83%; $P < .0001$), and the trial was stopped at the interim review due to treatment superiority. This allowed all patients in the placebo arm to receive treatment, but confounded the OS analysis.[4] In the phase 3 SSGXVIII/AIO trial, 398 patients at high risk of recurrence following complete resection of primary GIST were randomly assigned to receive 12 or 36 months of imatinib therapy (400 mg/day). At a median follow-up of 54 months, death or disease recurrence had occurred in 42.2% of patients in the 1-year arm, compared with 25.2% of patients in the 3 year-arm.[19] These results indicate that longer duration of imatinib therapy can improve survival outcomes in the adjuvant setting, similar to the advanced/unresectable setting.

Evidence supporting continuous imatinib treatment

Advanced, unresectable, or metastatic GIST

The results discussed above suggest that longer imatinib treatment is associated with improved outcomes for patients with GIST. However, they do not indicate that continuous, chronic treatment is needed or beneficial for patients (as is the case in chronic myeloid leukemia[20]), or that treatment interruptions may be detrimental. To assess the necessity of continued imatinib therapy, the BFR14 trial compared PFS in 58 patients with advanced/unresectable GIST who achieved disease control for 1 year (while on imatinib 400 mg/day) and were then randomized to stop or continue imatinib treatment until disease progression (Table 1).[10] Results showed that median PFS was significantly longer in the continuation group (18 months) than in the interruption group (6.1 months; $P < .0001$). In addition, fewer patients experienced disease progression in the continuation group (31%) than in the interruption group (81%; $P < .0001$; follow-up > 1 year).[10] For patients who stopped treatment, median time to progression (TTP) after imatinib interruption was 6 months, and more than 75% of patients had relapsed 1 year after treatment interruption.[10] Notably, adverse events (AEs) were manageable and overall quality of life was not significantly different between the 2 patient groups. Data from this clinical trial thus suggest that imatinib interruption is associated with an increased risk of disease progression in patients with advanced/unresectable GIST, and that longer, continuous courses of therapy are safe.

In an extension of the BFR14 trial, Le Cesne et al followed 50 patients who were randomly assigned to ei-

TABLE 2 Recurrence-free survival in patients with high-risk GIST who received imatinib for a longer duration in the adjuvant setting

Treatment	Study	Duration of treatment, y	RFS Follow-up, % 1-year	2-year	3-year	5-year
Imatinib	DeMatteo et al[4]	1	98	–	–	–
	Joensuu et al[8]	1	–	–	–	48
	Joensuu et al[8]	3	–	–	–	66
Placebo	DeMatteo et al[4]	1	83	–	–	–

Abbreviations: GIST, gastrointestinal stromal tumors; RFS, recurrence-free survival.

ther stop or continue imatinib treatment after experiencing controlled, nonprogressing disease for 3 years while taking imatinib.[11] After a median follow-up of 35 months, their findings revealed that 1- and 2-year PFS rates were significantly longer in the continuation group (92% and 80%) than the interruption group (32% and 16%; $P < .0001$), respectively (Table 1). Median TTP was 9 months (95% CI, 5.0-12.3) in the interruption arm, but was not reached in the continuation arm ($P < .0001$). Of note is that there was no significant difference in AEs grade ≥ 3 between the 2 groups; the most frequent AEs were neutropenia, asthenia, rash, and edema.[10,11]

Another extension study of the BFR14 trial was also undertaken in which Ray-Coquard et al randomly assigned 21 patients with controlled, nonprogressing, advanced or metastatic GIST to either stop or continue imatinib after 5 years of treatment.[12] After a median follow-up of 1 year, 45.5% of patients who discontinued imatinib after 5 years of treatment exhibited GIST progression, whereas none of the patients who continued treatment experienced disease progression ($P = .035$; Table 1). Moreover, 1 year after randomization of patients to the 1-, 3-, or 5-year continuation arm, the relapse rates were 20%, 8%, and 0, respectively,[10-12] indicating that prolonging imatinib therapy can significantly reduce the risk of disease progression and thus improve survival. Conversely, interrupting imatinib treatment should not be recommended.

Ray-Coquard et al also reported that all patients whose GIST progressed after interrupting imatinib treatment regained tumor control upon reintroduction of the same dose of imatinib.[12] Similarly, Domont et al showed that 96% of patients who experienced GIST progression after interrupting imatinib treatment regained tumor control following reintroduction of imatinib.[13] However, their results also showed that although patients remained sensitive to imatinib treatment following prolonged imatinib exposure and treatment interruption, the tumor response obtained upon reintroduction was not as robust as the initial response (prior to treatment interruption). Only 41.2% of patients who achieved complete response (CR) with initial imatinib treatment achieved a new CR as best response after reintroduction of imatinib. Likewise, only 56% of patients who achieved PR with initial treatment achieved a PR again upon reintroduction.[13]

Altogether, these results highlight a positive correlation between the duration of imatinib treatment and clinical benefit. They also demonstrate that interruption of imatinib treatment leads to rapid disease progression, regardless of the duration of prior imatinib therapy, and that patients whose GIST progress while off treatment are unlikely to regain the same level of disease control after imatinib reintroduction. Accordingly, interruption of imatinib treatment should be avoided, and longer or continuous treatments should be supported and favored to maximize clinical outcomes in patients with unresectable, advanced, or metastatic GIST.

Adjuvant setting following resection of primary GIST

The benefit of continuous imatinib treatment has also been demonstrated in the adjuvant setting (Table 2). In the phase 3 ACOSOG Z9001 trial, DeMatteo et al randomized 713 patients to receive adjuvant imatinib or placebo treatment after complete resection of primary GIST.[4] After 1 year of treatment, the RFS rate was 98% in the imatinib group, compared with 83% in the placebo group (hazard ratio [HR], 0.35; 95% CI, 0.22-0.53; $P < .0001$).[4] Although the trial was not designed to evaluate subsets of patients, post hoc analyses based on 3 tumor size subgroups (≥ 3 cm but < 6 cm; ≥ 6 cm but < 10 cm; ≥ 10 cm) revealed that RFS was longer in the imatinib group, regardless of tumor size at baseline. However, the difference between the imatinib and placebo group was more pronounced in the high-risk subgroup with tumors ≥ 10 cm (HR, 0.29; 95% CI, 0.16-0.55; $P < .0001$), which is significant given that in the absence of adjuvant treatment, high-risk patients have a 50% chance of developing recurrent GIST within 2 years.[4] Importantly, the rate of GIST recurrence in the imatinib group increased by about 6 months following completion of imatinib adjuvant therapy,[4] consistent with PFS and TTP values of 6.1 and 6 months, respectively, seen in patients with advanced/metastatic GIST upon imatinib cessation.[10] These results thus indicate rapid disease recurrence

after completion of 1 year of adjuvant imatinib therapy and cessation of treatment, which provided the rationale to evaluate the efficacy of longer imatinib adjuvant treatments in separate trials.

In the phase 3 SSGXVIII/AIO trial, Joensuu et al randomized 400 patients at high risk of recurrence to 1 year or 3 years of adjuvant imatinib following complete resection of primary GIST.[8] Their findings revealed superior RFS (HR, 0.46; 95% CI, 0.32-0.65; $P < .001$) and OS (HR, 0.45; 95% CI, 0.22-0.89; $P < .02$) for patients assigned to the 3-year arm. Indeed, 5-year RFS and OS rates were 65.6% and 92.0% in the 3-year imatinib group, compared with 47.9% ($P < .001$) and 81.7% ($P = .02$) in the 1-year imatinib group, respectively.[8] These results, combined with those described above, clearly demonstrate that a longer imatinib treatment improves clinical outcomes in the adjuvant setting, similar to the advanced/metastatic setting.

In both adjuvant trials described here, imatinib was well tolerated.[4,8] Grade 1 and 2 AEs were common (eg, anemia, leukopenia, granulocytopenia, diarrhea, nausea, flatulence, headache, rash, edema, fatigue, myalgia or arthralgia, elevated blood lactate dehydrogenase, and elevated serum creatinine), but grade 3 and 4 AEs occurred in fewer than one-third of patients treated with imatinib and were not exacerbated by longer courses of treatment. Overall, the data confirm that continuous imatinib therapy is feasible and safe, and that it can improve clinical outcomes in both the adjuvant and advanced/metastatic setting.

Feasibility of long-term imatinib treatment

The benefit of continuous imatinib therapy for up to 3 and 5 years has been demonstrated in the adjuvant and advanced/metastatic setting, respectively. However, the optimal duration of imatinib treatment remains unknown. Additional studies have been undertaken to evaluate the safety and efficacy of longer courses of imatinib in patients and to determine the feasibility of long-term imatinib treatment in both settings. In the adjuvant setting, Joensuu et al initially reported no new treatment-related AEs in patients with GIST who received 3 years of adjuvant imatinib following complete resection, compared with those who received 1 year of treatment.[8] Throughout the SSGXVIII/AIO trial, imatinib was well tolerated and discontinuation rates for reasons other than recurrence were relatively low in both treatment groups: 12.6% in the 1-year arm and 25.8% in the 3-year arm.[8] By comparison, rates of treatment discontinuation due to treatment-related AEs were 7.5% in the 1-year arm and 13.6% in the 3-year arm.[8] Considering that 7.5% of patients discontinued treatment because of AEs in the first year, these findings suggest that the discontinuation rate slowed down in years 2 and 3.

Based on these positive results, PERSIST-5, a phase 2 trial designed to evaluate the efficacy and safety of 5 years of adjuvant imatinib, has been initiated.[21] This ongoing trial will provide further information about the feasibility, safety, and efficacy of long-term adjuvant imatinib therapy in patients at significant risk of recurrence following complete resection of primary GIST.

In the advanced/metastatic setting, von Mehren et al followed patients with unresectable GIST through serial extensions of the B2222 trial.[14] Of the 147 patients initially enrolled, 56 continued imatinib therapy beyond 3 years. After a median follow-up of 9.4 years, 46% remained on continuous imatinib treatment, whereas 37.5% withdrew due to GIST progression. Importantly, imatinib was generally well tolerated throughout the extension phase and no new AEs were observed. Moreover, the estimated 9-year OS rate was 35% for all patients, 38% for patients with CR/PR, 49% for those with SD, and 0% for those with progressive disease.[14] These data suggest that long-term therapy with imatinib is feasible, safe, and perhaps effective at improving survival in patients with advanced GIST that respond to imatinib treatment.

In a similar study, Blanke et al followed 695 patients with nonprogressing, metastatic, or unresectable GIST who were initially enrolled in the S0033 trial and were allowed to stay on imatinib (400 mg once or twice daily) indefinitely.[15] Median follow-up was 8.8 years, during which no new AEs were observed. Estimated 8-, 9-, and 10-year OS rates were 31% (95% CI, 27-34), 26% (95% CI, 23-39), and 21% (95% CI, 17-25), respectively, and were not affected by treatment dose.[15] These results demonstrate that some patients with advanced GIST can survive for periods that approach and even exceed a decade when treated with imatinib, without emergence of additional toxicities.

Factors predicting treatment response

There are, of course, certain factors that can affect a patient's response to imatinib and, consequently, his/her outcomes. Over 100 different mutations have been identified in GIST and studies have shown that patients with GIST characterized by KIT exon 9 mutations are usually less responsive to imatinib than patients with KIT exon 11 mutations and may require a higher dose (800 mg/day) to experience improved survival.[22-24] On the other hand, patients with GIST characterized by the D842V mutation in platelet-derived growth factor receptor alpha (PDGFRA) exon 18 do not respond to currently approved TKI and are thus unlikely to benefit from longer imatinib treatment.[8,25-28] Similarly, patients with wild-type GIST

(without mutations in KIT or PDGFRA) respond poorly to imatinib and would likely not benefit from extended therapy. This group includes a recently identified subset of GIST with succinate dehydrogenase deficiency that exclusively affects the stomach, predominates in pediatric GIST, can metastasize to the lymph nodes, and for which aggressiveness cannot be predicted based on tumor size and mitotic index (compared with typical GIST).[29,30]

Genotyping has been used in various clinical trials to identify patients who are good candidates for imatinib therapy and/or determine optimal dosing to ensure optimal management of the disease. Similarly, genotyping may be useful in the real-world setting to identify patients who will benefit from prolonged imatinib treatment, as it would allow oncologist to provide adequate treatment early on to further improve disease control.

Conclusions

Imatinib is the standard of care for patients with GIST and is approved as first-line treatment for advanced, unresectable or metastatic GIST, as well as adjuvant therapy following resection of primary GIST.[6] The NCCN guidelines currently recommend treating advanced/unresectable GIST with imatinib until disease progression. In the adjuvant setting, a minimum of 3 years of treatment for patients at high risk of recurrence is advised.[16] These recommendations are based on clinical data that showed significant improvement of survival outcomes in intermediate- to high-risk patients who received longer treatments.

The evidence discussed herein reiterates the importance and benefits of chronic, continuous, uninterrupted imatinib therapy in patients with advanced, unresectable or metastatic GIST. In addition, ongoing studies are evaluating whether increasing the duration of adjuvant imatinib treatment beyond 3 years can further improve clinical outcomes in patients who undergo resection of primary GIST. In both settings, longer-term imatinib therapy correlated with prolonged PFS/RFS, without raising new safety concerns. These data suggest that most patients with GIST are able to tolerate longer-term imatinib treatment and could thus benefit from longer therapy. This is an important point, especially when considering that recurrence/progression rates increased only 6 months after imatinib discontinuation in both settings, suggesting rapid progression following treatment TKI interruption.

Overall, the data published to date show that extended imatinib treatments improve clinical benefits for patients with GIST, treatment interruptions should be avoided, and long-term treatment is well tolerated in both advanced disease and adjuvant settings. The absence of new or worsening AEs over extended treatment periods is important as it suggests that treatment-related toxicity is not cumulative, a key factor in the implementation or development of chronic treatments.

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