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review

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Imatinib rechallenge in patients with advanced gastrointestinal stromal tumors

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Background: Imatinib is the standard of care for patients with advanced gastrointestinal stromal tumors (GIST).
Design: This article reviews recent data on the impact of imatinib treatment interruption and subsequent rechallenge in patients with advanced GIST.
Results: The randomized BFR14 trial showed that (i) interruption of imatinib after 1, 3, or 5 years of treatment in patients with nonprogressive GIST was associated with a high risk of progression even in patients with a complete response; (ii) rechallenge with imatinib restored tumor control in most patients, but the tumor response seldom reached that before treatment interruption; (iii) patients receiving continuous imatinib had a high rate of prolonged tumor control, which increased with longer imatinib treatment. The findings in the metastatic setting have important implications regarding the duration of adjuvant imatinib in GIST.
Conclusions: Discontinuation of imatinib in responding patients with advanced GIST is associated with a high risk of progression and is therefore not recommended. Although rechallenge is a strategy for treating patients who relapse after stopping imatinib, suboptimal tumor response indicates that continuous kinase suppression is necessary to achieve the best clinical outcome. Three-year adjuvant imatinib is recommended for patients with resected 'high-risk' GIST; however, a longer duration may provide additional benefits.
Key words: adjuvant, advanced, gastrointestinal stromal tumor, imatinib, rechallenge, resistance

introduction

Historically, patients with advanced gastrointestinal stromal tumors (GIST) had a very poor prognosis because of the limited surgical options and the generally poor response of GIST to conventional chemotherapy and radiotherapy [1]. The introduction of imatinib mesylate has improved the clinical outcome of these patients significantly; now a median overall survival (OS) of 4–5 years in the metastatic phase may be expected [1]. Imatinib is a small molecule inhibitor of tyrosine kinase receptors, including stem cell factor receptor KIT and the platelet-derived growth factor receptor alpha, and mutations in either of these kinases are found in the majority (~85%) of GIST patients [2]. Based on its efficacy, which has been demonstrated in several phase II and III trials in the advanced/metastatic setting [3–6], imatinib is now the standard of care first-line treatment in advanced GIST [7, 8].

In patients with advanced GIST, current treatment guidelines recommend that imatinib therapy be continued indefinitely or until progressive disease (PD) occurs [7–12]. Due to its limited toxicity and prolonged tumor control in most patients with GIST, chronic administration of imatinib is generally feasible. However, long-term treatment with imatinib may be associated with several potential problems. First, serious adverse events (AEs) or minor but chronic AEs, although occurring in only a minority of patients, may prompt a patient to request a 'treatment holiday' or treatment interruption. Second, some patients may develop resistance to imatinib over time, even after achieving tumor responses. In clinical studies of imatinib in patients with advanced GIST, resistance occurred at a median time of 18–26 months [4, 5]. Resistance may be due to decreased imatinib exposure after long-term treatment [13, 14]; however, it results most often from the acquisition of secondary *KIT* mutations [15, 16]. A central question is whether treatment interruption favors or limits the selection of these imatinib-resistant secondary mutations. Finally, adherence to self-administered imatinib can be a challenge for patients on chronic therapy, as reported for patients with GIST who were taking imatinib long term [17]. Imatinib-related AEs and cost are key factors that may influence a patient's decision to discontinue imatinib [18, 19]. Because of these potential problems, it is important to investigate whether imatinib can be safely interrupted in patients with nonprogressing advanced GIST, whether this interruption affects the emergence of imatinib resistance, and whether patients with PD after treatment interruption may derive clinical benefit from imatinib rechallenge.

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Imatinib is also indicated for patients in the adjuvant setting after complete resection of primary, localized KIT+ GIST [20]. Adjuvant imatinib has been demonstrated to delay recurrence significantly when given for a year, compared with placebo ($P < 0.0001$) [21], and to significantly prolong OS and recurrence-free survival (RFS) when given for 3 years, compared with 1 year of treatment [22]. It remains unclear whether prolonged use of adjuvant imatinib beyond 3 years may be required to prevent GIST recurrence. Duration of adjuvant imatinib therapy as well as the efficacy of imatinib rechallenge for treating recurrence after completion of adjuvant imatinib therapy are important topics that are currently under intense investigation.

is it safe to interrupt imatinib treatment in responding patients?

The phase III BFR14 trial conducted by the French Sarcoma Group investigated the effect of interrupting therapy after 1, 3, and 5 years of daily treatment with 400 mg of imatinib in patients with advanced GIST (Figure 1) [10, 11, 24]. The study was originally designed to compare progression-free survival (PFS) of patients who underwent continuous versus interrupted imatinib beyond 1 year of treatment [10]. Interruption of therapy after 1 year in responding patients resulted in rapid PD. Of 58 randomized patients, 26 of 32 (81%) patients in the treatment interruption arm experienced PD after treatment interruption, compared with 8 of 26 patients (31%) in the imatinib continuation arm, at the time of data cut-off (October 2005) ($P \leq 0.0001$) [10]. Median PFS after randomization was 6.1 months in the interruption arm and 18 months in the continuation arm ($P \leq 0.0001$) [10].

To examine whether a longer course of imatinib treatment might affect PFS, the study protocol was amended to randomize the 50 responding patients to continue or stop imatinib after 3 years of therapy [11]. Similarly, imatinib interruption resulted in rapid progression with a median PFS of only 9 months after random assignment to the interruption group, while median PFS was not reached in the continuation group ($P < 0.0001$) [11]. The rate of 2-year PFS was also significantly lower among patients with interrupted therapy (16%) compared with those receiving continuous therapy (80%; $P < 0.0001$) (Figure 2) [11]. It is important to note that the significantly increased risk of relapse associated with imatinib interruption after 1 or 3 years of imatinib treatment was observed even in patients who achieved complete response (CR) before randomization [10, 11]. After imatinib interruption, PFS of patients with CR was similar to that of patients with assessable residual tumor in this small series [10].

Preliminary results of continuous versus interrupted imatinib after 5 years of therapy were reported at the 2010 American Society of Clinical Oncology (ASCO) annual meeting [24]. A total of 21 patients with tumor response or stable disease (SD) after 5 years of imatinib treatment were randomized; 5 of 11 patients in the interruption arm relapsed after a median follow-up of 12 months from randomization compared with no relapse among the 10 patients in the continuation arm ($P = 0.035$). Updated results of the BFR14 trial were reported at ASCO 2011 (Table 1) [23]. Similar to patients randomized at 1 and 3 years, imatinib interruption resulted in a lower PFS compared with imatinib continuation in patients randomized at 5 years (median, 13 months versus not reached) [23].

An example of rapid disease recurrence associated with imatinib interruption after 7 years of treatment was recently illustrated in a case study [25]. In this report, a patient with metastatic GIST achieved a CR 2 months after initiation of imatinib therapy, and the CR was maintained while the patient was on imatinib treatment [25]. Interruption of therapy after 7 years resulted in rapid extensive disease recurrence within 9 months, suggesting that imatinib should be continued even in the absence of evidence of tumor progression [25].

One of the reasons that patients on long-term imatinib treatment may request treatment interruption is that some

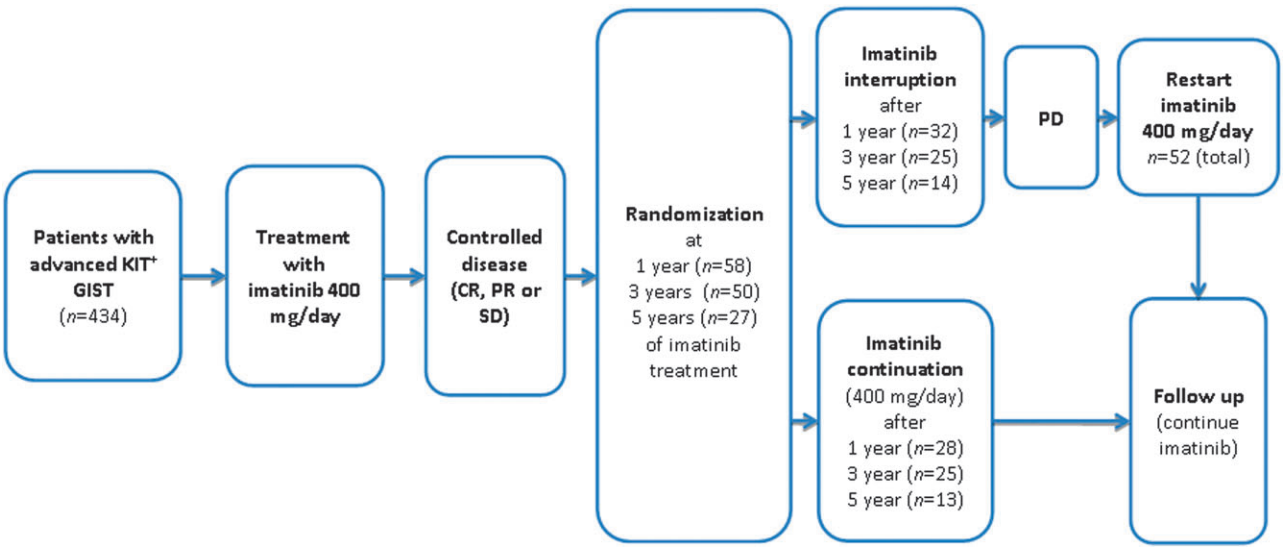

Figure 1. Trial design of the BFR14 French Sarcoma Group randomized phase III trial in patients with advanced GIST. Response was defined according to RECIST [10, 11, 23]. CR, complete response; GIST, gastrointestinal stromal tumors; PD, progressive disease; PR, partial response; SD, stable disease.

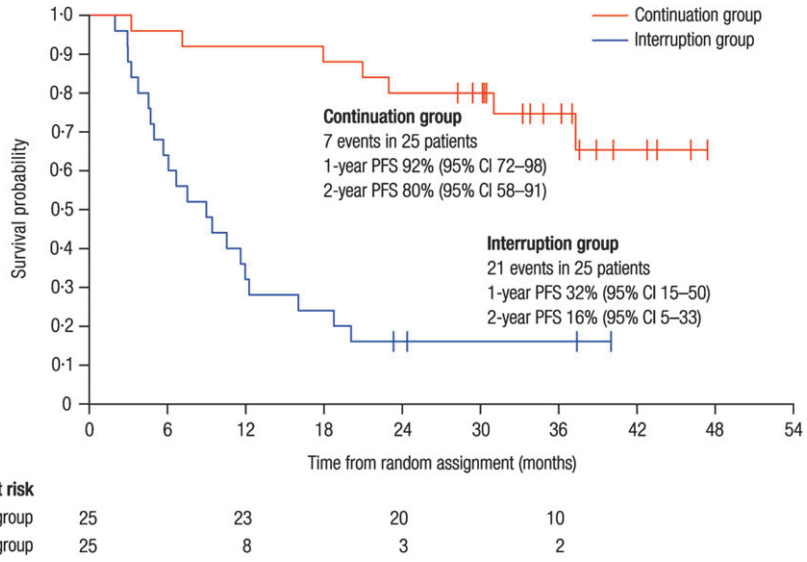

Figure 2. Comparison of PFS in nonprogressing patients with advanced gastrointestinal stromal tumors randomized to imatinib treatment interruption or continuation at 3 years in the BFR14 French Sarcoma Group randomized Phase III trial. PFS was calculated from the randomization point in each group [11]. CI, confidence interval; PFS, progression-free survival.

Table 1. Updated results of PFS and tumor control of patients with advanced GIST in the BFR14 French Sarcoma Group randomized phase III trial

Parameter	Years of imatinib treatment before randomization		
	1 year	3 years	5 years
Randomized patients[a]			
All (interruption/continuation)	58 (32/28)	50 (25/25)	27 (14/13)
Median follow-up, months			
All	74	47	18
Median PFS, months			
Interruption/continuation	7/29	9/NR	13/NR
Patients with tumor control after imatinib reintroduction			
Tumor control/imatinib reintroduction	23/25	20/20	6/7
Imatinib-resistant PFS at 2 years			
Interruption/continuation	60/62	87/80	NE

Courtesy of Dr Axel Le Cesne.
[a]Patients were randomized to treatment interruption or treatment continuation after 1, 3, or 5 years of treatment with imatinib (400 mg/day). For patients who progressed after discontinuation of imatinib, imatinib treatment was restarted, and tumor control was assessed [23].
GIST, gastrointestinal stromal tumors; NE, not evaluated; NR, not reached; PFS, progression-free survival.

experience treatment-related AEs (even of limited magnitude) that may affect their quality of life. Although the number of patients was limited, interruption of imatinib treatment after 1 year did not significantly improve patients' global health status, functional status, or symptom scores in the BFR14 trial, as measured by the cancer-specific European Organization for Research and Treatment of Cancer Core Quality-of-Life Questionnaire (EORTC QLQ-C30) [10, 26]. In this case, treatment interruption was not associated with a major improvement of quality of life of patients in this study [10, 26].

In patients with nonprogressive GIST, interruption of imatinib after 1, 3, or 5 years of treatment is associated with a high risk of progression, irrespective of the pattern of initial radiological response or the pattern of radiological response at the time of randomization. These results suggest that imatinib can effectively control tumor progression but may not eliminate tumor cells in patients with advanced GIST. Even patients in complete remission may have residual tumor, albeit invisible by standard morphological criteria. Therefore, it is not recommended to interrupt imatinib in responding patients, including those with a CR.

do progressing patients respond to imatinib rechallenge after imatinib interruption?

The efficacy of imatinib rechallenge in patients with PD after treatment interruption was also studied in the BFR14 trial [10, 11, 23, 24]. Among the 26 patients who discontinued imatinib after 1 year and then progressed, all restarted imatinib treatment at 400 mg/day; the majority of these patients (92%) achieved tumor control [10]. Similarly, the majority of patients with PD after treatment interruption at 3 and 5 years experienced CR, partial response (PR), or SD after imatinib reintroduction (Table 1) [11, 23, 24]. Overall, imatinib rechallenge led to tumor control in 94% (49/52) of patients randomized at 1, 3, or 5 years of initial imatinib treatment (Table 1) [23]. In the aforementioned case report, upon rechallenge with imatinib after interruption of 7 years of treatment, the patient also rapidly achieved another CR [25].

However, patients with PD following imatinib interruption were not always able to achieve the same degree of tumor control as they had before interrupting therapy. For example, of

patients randomized to the interruption arm at 1, 3, or 5 years during the BFR14 trial, only 41.7% of patients with a CR and 56% of patients with a PR observed at the time of randomization achieved a new CR and PR, respectively, as best response when imatinib was restarted [27]. Because tumor volume is one of the predictive factors for PFS and OS in patients with advanced GIST [28, 29], these results suggest that the response to imatinib rechallenge after treatment interruption may not be optimal.

An important issue regarding imatinib interruption is whether it may affect the incidence of secondary resistance to imatinib. An analysis of the BFR14 trial compared the time to first progression in patients on continuous imatinib versus the time to second progression in patients after imatinib rechallenge. Imatinib-resistant PFS was not significantly different between the continuation and the interruption groups for patients randomized to interruption at 1, 3, or 5 years (Table 1) [10, 11, 23], suggesting a lack of effect on the imatinib-resistance selection process by treatment discontinuation. However, these results need to be interpreted with caution, given the limited power of analysis due to the small number of patients.

Although treatment interruption may not affect the emergence of imatinib resistance, time to progression after imatinib interruption influenced the likelihood of developing secondary resistance to imatinib [30]. In a subgroup analysis of the BFR14 trial, patients who relapsed rapidly after stopping imatinib were more likely to show resistance to imatinib upon rechallenge than those who did not relapse as quickly after interruption [30]. Interestingly, if patients remained on continuous imatinib therapy for a longer duration, they were less likely to develop secondary resistance to imatinib.

In patients randomized to the continuation arm, the 2-year PFS after randomization increased from 62% after 1 year of imatinib to 80% after 3 years (Figure 3) and 100% after 5 years of treatment (Table 1) [11, 23]. Although these results clearly reflect the selection for patients with prolonged disease control in the 3- and 5-year arms, it also indicates that the emergence of secondary resistance decreases over time, leaving open the possibility of very long-term tumor control in a significant proportion of patients with advanced GIST treated with imatinib.

Based on the above data, rechallenge with imatinib induced tumor control in the majority of patients with progression after interrupting therapy, but the volumetric tumor response achieved after reintroduction is often inferior to that achieved before interruption [27]. In comparison, patients who received continuous imatinib had a high rate of tumor control, and this rate increased with longer imatinib treatment. These results indicate that even though imatinib rechallenge is feasible, it is not recommended to discontinue imatinib treatment in patients with advanced GIST unless they experience substantial and unmanageable toxic effects.

implications for imatinib treatment in the adjuvant setting

The findings of the BFR14 trial have important implications in regard to the duration of imatinib treatment of patients with GIST in the adjuvant setting. The phase III American College of Surgeons Oncology Group (ACOSOG) Z9001 study showed that 1-year adjuvant imatinib treatment was significantly more effective than placebo in reducing recurrence in patients with completely resected primary GIST [21]. The 1-year rate of RFS

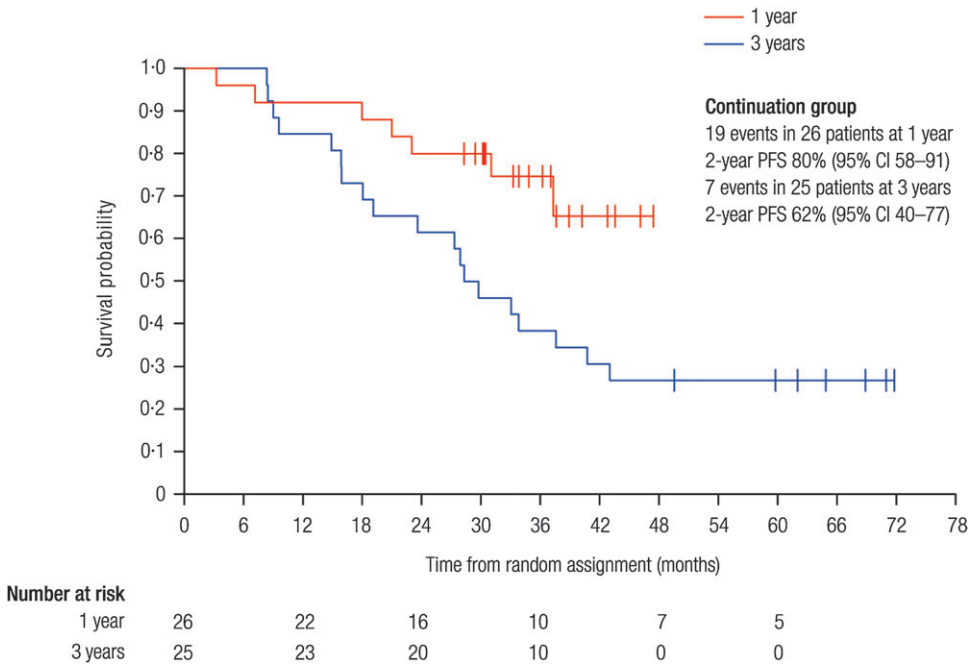

Figure 3. Comparison of PFS in nonprogressing patients with advanced gastrointestinal stromal tumors randomized to the imatinib continuation group at 1 or 3 years in the BFR14 French Sarcoma Group randomized phase III trial. PFS was calculated from the randomization point in each group [11]. CI, confidence interval; PFS, progression-free survival.

was 98% for patients receiving imatinib compared with 83% for patients receiving placebo [hazard ratio (HR) 0.35, $P < 0.0001$] [21]. However, the difference in RFS between patients on adjuvant imatinib and those on placebo appeared to become smaller over time [21]. In addition, the single-arm phase II ACOSOG Z9000 study reported rates of RFS of 94% at 1 year, 73% at 2 years, and 61% at 3 years in patients at high risk of recurrence after 1 year of adjuvant imatinib treatment [31], suggesting that 1-year adjuvant imatinib may only postpone relapse. Considering the results of the BFR14 trial, which suggested that continuous imatinib treatment is necessary to control residual disease in patients with advanced GIST, it was hypothesized that prolonged use of adjuvant imatinib beyond 1 year might be required to reduce the risk of recurrence further.

Indeed, the phase III study conducted by the Scandinavian Sarcoma Group and the Sarcoma Group of the Arbeitsgemeinschaft Internistische Onkologie (AIO; SSGXVIII/AIO study) recently demonstrated that 3 years of adjuvant imatinib, compared with 1 year of imatinib, can significantly reduce the risk of recurrence and improve OS in patients with KIT+ GIST at high risk of recurrence [22]. The final results of the study presented at ASCO 2011 [22] showed that at a median follow-up of 54 months, RFS was significantly longer for patients on 3-year adjuvant imatinib therapy ($n = 198$) than for those on 1-year adjuvant imatinib therapy [$n = 199$; HR 0.46, 95% confidence interval (CI) 0.32–0.65, $P < 0.0001$]. The estimated 5-year RFS was 65.6% for patients on 3-year therapy versus 47.9% for those on 1-year therapy. This RFS benefit has translated into a significant OS benefit: patients receiving 3-year adjuvant imatinib had significantly longer OS than those receiving 1-year adjuvant imatinib (HR 0.45, 95% CI 0.22–0.89, $P = 0.019$). The estimated 5-year OS was 92.0% for patients on 3-year adjuvant imatinib versus 81.7% for those on 1-year treatment. The results of the SSGXVIII/AIO trial are changing the therapeutic standard in the management of GIST: patients who have a high estimated risk of recurrence after surgery now should receive 400 mg/day of imatinib as adjuvant treatment of a minimum duration of 3 years [32].

Even with the results of the SSGXVIII/AIO trial, the optimal duration of adjuvant imatinib therapy continues to be unknown. The parallel inclination of the slopes of the RFS curves in the 1-year and the 3-year arms in the SSGXVIII/AIO trial [22] suggest that 3-year adjuvant imatinib may only delay recurrence and not prevent it. Adjuvant treatment duration of >3 years may be needed to further reduce or even prevent recurrence. In the BFR14 study, none of the patients who are on continuous imatinib for >5 years has progressed or developed secondary resistance to imatinib [23]. In another study of advanced GIST patients on long-term imatinib (B2222 study), the risk of progression drastically decreased after 6 years of imatinib therapy: the probability of progression decreased from 48.7% after >4–6 years of therapy to 5.3% after >6–8 years of therapy [29]. Moreover, imatinib was well tolerated in patients on long-term therapy, and 35% of patients with advanced GIST survived at the 9-year follow-up in the B2222 study. Therefore, it is possible that in the adjuvant setting, a minimum duration of 5 years would allow the selection of a patient population who are more likely to have sustained disease control. Post-resection Evaluation of Recurrence-free Survival for gastroIntestinal Stromal Tumors (PERSIST-5) is a phase II trial that will evaluate the efficacy of 5 years of adjuvant imatinib therapy (400 mg/day) in patients with completely resected GIST (R0) with significant risk for recurrence; the primary end point is RFS. The PERSIST-5 trial is currently actively recruiting patients in the United States [33].

As in the metastatic setting, it is also important to ascertain whether imatinib rechallenge would provide clinical benefit for patients in the adjuvant setting. As mentioned previously, data from the BFR14 trial indicate that if a prior treatment with imatinib was interrupted in metastatic patients with controlled disease (i.e. CR, PR, or SD according to RECIST), the subsequent reintroduction of imatinib treatment at the time of progression enables tumor control in 94% of patients [23]. However, in some cases, the response to imatinib rechallenge was not as robust as that before treatment interruption [27]. Whether this also holds true in the adjuvant setting is unknown. The recently reported subgroup analysis of the SSGXVIII/AIO trial showed that imatinib rechallenge for treating GIST recurrence achieved a clinical benefit rate (CBR) of 84.8% (CR 32.6%, PR 30.4%, SD 21.7%) in patients with prior adjuvant imatinib treatment; the CBR was comparable between patients who received adjuvant imatinib for 1 year or 3 years [34]. These results suggest that most patients given a diagnosis of recurrent GIST after having received imatinib in the adjuvant setting may respond to imatinib rechallenge. However, a longer follow-up to this subgroup of patients is needed to evaluate the impact of previous adjuvant therapy on the time to secondary resistance on imatinib rechallenge. In addition, it is unclear in the analysis at what point time these patients developed GIST recurrence: during adjuvant therapy, within a year, or longer than a year after completing adjuvant therapy. Evaluating the efficacy of imatinib rechallenge in relation to the timing of GIST recurrence may identify the most appropriate patient population for imatinib rechallenge. An alternative treatment strategy, such as imatinib dose escalation, may be needed in patients who do not respond well to rechallenge with standard dose imatinib.

Another large, randomized controlled phase III trial, the EORTC 62024 trial, is in progress and compares 2 years of adjuvant imatinib with observation alone in patients with complete resection of localized GIST who are at intermediate or high risk of recurrence; the primary end point is time to secondary resistance [35]. This study was closed for inclusion in October 2008 and was estimated to be completed during the first quarter of 2012. Because the comparator arm is observation, the comparison of time to secondary resistance to imatinib between patients with or without adjuvant imatinib treatment may provide a more definitive conclusion regarding the impact of adjuvant therapy on the sensitivity of imatinib rechallenge.

conclusions

Collectively, data from the BFR14 trial indicate that interrupting imatinib therapy in patients with advanced GIST who are responding to treatment leads to a higher rate of PD than maintaining therapy. Rechallenge with imatinib following cessation can provide clinical benefits to progressing patients with metastatic GIST; however, quality of tumor response may

not be optimal after imatinib reintroduction. In addition, long-term follow-up results from the BFR14 and B2222 studies show that the longer patients stay on continuous imatinib therapy, the less likely they are to develop PD. Thus, imatinib should be given continuously, as tolerated, in the population of nonprogressing advanced or metastatic GIST patients.

In the adjuvant setting, although the optimal duration of adjuvant imatinib therapy has not been determined, the results of the SSGXVIII/AIO trial now support that adjuvant imatinib should be recommended for at least 3 years in GIST patients at considerable risk for recurrence. As reflected in the updated National Comprehensive Cancer Network guidelines [32], this treatment regimen represents the new gold standard for patients with resected 'high-risk' GIST.

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