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CURRENT OPINION

Extended Adjuvant Therapy with Imatinib in Patients with Gastrointestinal Stromal Tumors

Recommendations for Patient Selection, Risk Assessment, and Molecular Response Monitoring

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Abstract On the basis of the recently published results of a clinical trial comparing 12 and 36 months of imatinib in adjuvant therapy for gastrointestinal stromal tumors (GISTs), which demonstrated clinical benefit of longer imatinib treatment in terms of delaying recurrences and improving overall survival, both the US Food and Drug Administration and the European Medicines Agency have updated their recommendations and approved 36 months of imatinib treatment in patients with v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KIT)-positive GISTs (also known as CD117-positive GISTs) at high risk of recurrence after surgical resection of a primary tumor. This article discusses patient selection criteria for extended adjuvant therapy with imatinib, different classifications of risk of recurrence, and assessment of the response to therapy.

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1 Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract, with a mean annual incidence of 10–15 cases per million people, affecting mainly older individuals at a median age of 55–65 years [1–4]. Radical surgery is the treatment of choice in primary resectable GISTs, but almost all GISTs are associated with a risk of recurrence, and approximately 40–50 % of patients with potentially curative resections develop recurrent or metastatic disease [5, 6]. Classic cytotoxic chemotherapy is ineffective in advanced cases. Radiotherapy has restricted efficacy in the management of GISTs, principally because the tumor location is surrounded by dose-limiting vital organs. The prognosis of patients with inoperable or metastatic GISTs was poor until the beginning of the 21st century, when significant progress in understanding the molecular pathogenesis of GISTs resulted in development of a treatment that has become a model of targeted therapy in oncology. The introduction of imatinib mesylate (Gleevec™ or Glivec®; Novartis), a small-molecule selective inhibitor of receptor tyrosine kinases, has revolutionized the treatment of GISTs, both in the adjuvant setting and in advanced (i.e., inoperable and/or metastatic) cases. On the basis of recently published results of a clinical trial comparing 12 and 36 months of adjuvant imatinib therapy [7], demonstrating clinical benefit of longer imatinib treatment in terms of delaying recurrences and improving overall survival (OS), both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have updated their recommendations and approved 36 months of imatinib treatment in patients with v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KIT)-positive GISTs (also known as CD117-positive GISTs) at

high risk of recurrence after surgical resection of the primary tumor.

2 Clinical and Molecular Features of GISTs

GISTs may originate anywhere in the gastrointestinal tract—most frequently in the stomach, followed by the small intestine. They comprise a heterogeneous group of tumors ranging from small lesions with clinically benign behavior to highly aggressive malignant tumors [8–10]. Metastases develop mainly in the liver or intraperitoneally and may even occur more than 10 years after surgery on the primary lesion, necessitating long-term follow-up of GIST patients [9, 11]. GISTs are believed to arise from progenitors related to the interstitial cells of Cajal, which are the pacemakers for peristalsis [12–14]. Approximately 85–95 % of GISTs express KIT, which is currently used for routine immunohistochemical diagnosis [15]. Other well-established immunohistochemical markers used for differential diagnosis include DOG1 [Discovered on GIST-1; encoded by the *ANO1* (anoctamin 1, calcium activated chloride channel) gene], CD34 (a hematopoietic progenitor stem-cell antigen), smooth muscle actin, S100 protein, and desmin (a muscle cell marker) [16–21]. Characteristic genomic alterations in both benign and malignant GISTs mainly involve chromosomal losses of 1p, 14q, and 22q. Additional cytogenetic abnormalities present in metastatic GISTs involve losses of chromosomes 13q, 15q, and 18, and partial deletions of 11p and 9p [including tumor suppressor genes *CDKN2A* (cyclin-dependent kinase inhibitor 2A) and *CDKN2B*], as well as gains of 5p, 8q, and 17q [22–28].

Approximately 75–80 % of sporadic GISTs harbor *KIT*-activating mutations, and another 5–13 % of sporadic GISTs carry platelet-derived growth factor receptor, alpha polypeptide (*PDGFRA*)-activating mutations [29, 30]. About two thirds of all mutations in GISTs occur at the 5′ end of *KIT* exon 11. Less common primary mutation sites in *KIT* include the 3′ end of exons 11 and 9. The most frequently mutated region in *PDGFRA* is exon 18, typically exhibiting the p.D842V substitution.

Approximately 10–15 % of GISTs do not present detectable mutations in *KIT* or *PDGFRA* [29–40]. *KIT/PDGFRA* wild-type GISTs arise mainly from the stomach and are characterized by distinct clinical and pathological features, including predominant incidence in young female patients, epithelioid morphology, frequent lymphovascular invasion and lymph node metastases, and unpredictable clinical behavior. Wild-type GISTs carry inactivating mutations in genes coding for mitochondrial succinate dehydrogenase (SDH) complex II subunits A, B, C, and D, which are components of the Krebs cycle and the respiratory chain. Additionally, this subgroup of GISTs express insulin-like growth factor 1 receptor (IGF1R). Wild-type GISTs are commonly associated with Carney's triad, Carney-Stratakis syndrome, or neurofibromatosis type 1 [41–51].

Table 1 Molecular classification of gastrointestinal stromal tumors (GISTs) according to v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (*KIT*) and platelet-derived growth factor receptor, alpha polypeptide (*PDGFRA*) mutational status

Genotype	Features
KIT mutations (75–80 % of sporadic GISTs)	
Exon 11	Most common mutation in sporadic GISTs (65–70 %); present in tumors localized at all gastrointestinal sites; best response to imatinib; also reported in familial GISTs
Exon 9	More common in GISTs originating from the small bowel/colon; intermediate/dose-dependent response to imatinib in advanced GISTs
Exon 13	Present in tumors localized at all gastrointestinal sites; observed clinical responses to imatinib; reported in familial GISTs; more often as secondary mutations in imatinib-resistant tumors
Exon 17	Present in tumors localized at all gastrointestinal sites; observed clinical responses to imatinib (except for p.D816V); reported in familial GISTs; more often as secondary mutations in imatinib-resistant tumors
PDGFRA mutations (5–13 % of sporadic GISTs)	
Exon 12	Present in tumors localized at all gastrointestinal sites; observed clinical responses to imatinib
Exon 14	Only a few cases described in the literature; more common in GISTs originating from the stomach
Exon 18	More common in GISTs originating from the stomach, usually with epithelioid morphology; often related to indolent clinical behavior; p.D842V is the most common and is resistant to imatinib; other exon 18 mutations are sensitive to imatinib
KIT/PDGFRA wild type	Frequent in pediatric GISTs; poor response to imatinib; typical for GISTs related to neurofibromatosis type 1, Carney's triad (gastric GIST + pulmonary chondroma ± paraganglioma), or Carney-Stratakis syndrome (GIST + paraganglioma, characterized by mutations in genes encoding SDH subunits SDHA, SDHB, SDHC, SDHD), and/or IGF1R expression

IGF1R insulin-like growth factor 1 receptor, *SDH* succinate dehydrogenase

Table 1 summarizes the most important molecular features of GISTs in terms of *KIT* and *PDGFRA* mutational status.

3 Imatinib Mesylate Therapy for Advanced GISTs

Imatinib mesylate was initially developed for the treatment of chronic myelogenous leukemia, to specifically inhibit the tyrosine kinase activity of breakpoint cluster region–c-abl oncogene 1, non-receptor tyrosine kinase (BCR–ABL) fusion oncoprotein [52]. However, in preclinical studies, it was demonstrated that imatinib also inhibited the activity of KIT, PDGFRA/B, ABL1, and ABL2 (also known as ARG) tyrosine kinases [53, 54], which encouraged examination of imatinib therapy for other neoplasms driven by constitutive receptor tyrosine kinase activation. The first report describing imatinib treatment in a GIST patient with multiple metastatic lesions demonstrated a dramatic response to this therapy [55]. As early as 2002, imatinib was registered for treatment of advanced GISTs (i.e. in metastatic and/or recurrent and/or inoperable disease). The results of several clinical trials confirmed the high efficacy of imatinib in the treatment of GISTs in the majority of patients with inoperable/metastatic disease [56–60], prolonging median survival from 10–19 months (historical data) to approximately 5 years. Two large, parallel, very similar international studies comparing a standard imatinib dose of 400 mg daily with a high dose of 800 mg daily demonstrated a similar response rate and OS with the two imatinib doses but better progression-free survival (PFS) in the high-dose treatment arm [60–62]. Moreover, data from these trials have shown that the response of GISTs with *KIT* exon 9 mutations depends on the dose of the drug, and that these patients benefit from a higher dose (800 mg daily) of imatinib, demonstrating significantly longer PFS (18 months) than patients receiving a standard dose of 400 mg daily (6 months) [39]. Unfortunately the spectacular activity of imatinib is time limited, and secondary resistance develops in the majority of patients [11, 61].

4 Adjuvant Imatinib Mesylate Therapy for GISTs

Although the treatment of choice in primary resectable localized GISTs is radical resection with negative margins, almost half of the patients ultimately develop recurrent or metastatic disease after potentially curative surgery [63]. Therefore, the idea of adjuvant therapy with imatinib after primary resection has been evoked to delay or prevent relapse and to prolong patients' survival. The role of imatinib therapy in the adjuvant setting has been evaluated in several phase II and III clinical trials, namely ACOSOG Z9000 [98] and Z9001 [76] (conducted by the American College of Surgeons Oncology Group), SSGXVIII/AIO [7, 65] (conducted by the Scandinavian Sarcoma Group and the Sarcoma Group of the Arbeitsgemeinschaft Internistische Onkologie XVIII), RTOG S0132 [95] (conducted by the Radiation Therapy Oncology Group), and EORTC 62024 (conducted by the European Organization for Research and Treatment of Cancer) [99]. Table 2 presents the most important clinical trials of adjuvant imatinib in GISTs. Data from the phase III ACOSOG Z9001 trial [76] evaluating 1 year of adjuvant therapy with imatinib 400 mg daily versus placebo in patients after microscopically radical (R0) resection of GISTs at least 3 cm in diameter showed a significant reduction in the risk of recurrence from 17 to 2 % at 1 year (during 20 months of follow-up) [$p = 0.0001$], with a hazard ratio (HR) of 0.35. Although the treatment was well tolerated, no significant impact on OS was demonstrated, thus implying that adjuvant imatinib delays rather than prevents relapse. The eligibility criteria for this trial were clearly inadequate because more than 40 % of patients had tumors between 3 and 6 cm in size, which in the majority were at low risk of relapse and did not require adjuvant therapy after surgery. Nevertheless, in 2008, imatinib was approved for use in adjuvant therapy after resection of primary GISTs in patients at significant risk of relapse. Importantly, the initial approval lacked definite guidance concerning the optimal duration of treatment and risk assessment criteria.

Only recent updates of the European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network (NCCN) guidelines have included the recommendation for 36 months of adjuvant imatinib therapy in adult patients with KIT-positive GISTs at high risk of relapse. However, the optimal duration of imatinib therapy is still unknown.

The latest FDA and EMA approvals for imatinib were based on the results of the SSGXVIII/AIO trial, which demonstrated that prolonged treatment extends both recurrence-free survival (RFS) and OS [64]. Data from the SSGXVIII/AIO trial, comparing 12 and 36 months of adjuvant imatinib treatment after resection of GISTs in patients with a high risk of recurrence, were first presented in 2011 at the 47th Annual Meeting of the American Society of Clinical Oncology. In the 36-month treatment arm, a significant improvement was observed in terms of both RFS (5-year RFS: 65.6 vs. 47.9 %; $p < 0.0001$) and OS (5-year OS: 92.0 vs. 81.7 %; $p = 0.01$; HR 0.45). The treatment was most effective in patients carrying *KIT* exon 11 mutations. The study demonstrated that prolonged imatinib treatment was generally well tolerated, and the most common adverse events included anemia, leukopenia, periorbital edema, fatigue, nausea, diarrhea, muscle cramps, and elevated blood lactate dehydrogenase levels.

Table 2 The most important clinical trials of adjuvant therapy with imatinib in gastrointestinal stromal tumors (GISTs)

Study	Study design	No. of patients	Major eligibility criteria	Results	
				Primary endpoint	Secondary endpoints
ACOSOG Z9000, DeMatteo et al. 2009 [98]	One arm, open, multicenter; imatinib 400 mg daily for 1 year	107	Primary GIST KIT-positive after radical resection; high risk of relapse: tumor size ≥10 cm *OR* tumor rupture *OR* <5 intraperitoneal metastases	OS at median follow-up of 4 years; 1-year OS: 99 %; 2-year OS: 97 %; 3-year OS: 97 %	RFS at median follow-up of 4 years; 1-year RFS: 94 %; 2-year RFS: 73 %; 3-year RFS: 61 %
Kang et al. 2009 [97]	One arm, open, multicenter, prospective; imatinib 400 mg daily for 2 years	47	Primary GIST with exon 11 *KIT* mutation after radical resection; high risk of relapse: tumor size ≥10 cm *OR* mitotic index ≥10/50 HPFs *OR* tumor size ≥5 cm and mitotic index ≥5/50 HPFs	RFS at median follow-up of 26.9 months; 1-year RFS: 97.7 %; 2-year RFS: 92.7 %	
Li et al. 2011 [93][a]	Open, non-randomized, prospective, one center; imatinib 400 mg daily for 3 years versus observation	56 (imatinib), 49 (observation)	Primary GIST KIT-positive after resection; intermediate or high risk of recurrence (NIH classification): tumor size >5 cm *AND/OR* mitotic index >5/50 HPFs	Significantly better RFS in the imatinib arm as compared with observation at median follow-up of 45 months (HR 0.188, 95 % CI 0.085–0.417; $p < 0.001$); 1-year RFS: 100 versus 90 %; 2-year RFS: 96 versus 57 %; 3-year RFS: 89 versus 48 %	Significantly decreased risk of death due to GIST with adjuvant imatinib therapy in comparison with observation at median follow-up of 45 months (HR 0.254, 95 % CI 0.070–0.931; $p = 0.025$)
Jiang et al. 2011 [92][a]	Non-randomized, one center, prospective; imatinib 400 mg daily for 5 years versus observation	35 (imatinib), 55 (observation)	Primary GIST KIT-positive after R0 resection; high risk of relapse (modified NIH classification)	Significantly better RFS with imatinib as compared with observation at median follow-up of 44.0 months (HR 0.122, 95 % CI 0.041–0.363; $p < 0.001$); 1-year RFS: 100 versus 70.9 %; 2-year RFS: 88.0 versus 37.8 %; 3-year RFS: 88.0 versus 27.5 %	
ACOSOG Z9001, DeMatteo et al. 2009 [76, 86]	Double-blind, placebo-controlled, randomized, multicenter; imatinib 400 mg daily versus placebo for 1 year	359 (imatinib), 354 (placebo)	Primary GIST KIT-positive after radical resection; tumor size ≥3 cm; low, intermediate, or high risk of relapse	Significant improvement in 1-year RFS in the imatinib arm (98 %) as compared with placebo (83 %); median follow-up time 19.7 months; HR 0.35; $p < 0.0001$	Lack of statistically significant difference in 1-year OS between study arms (HR 0.66; $p = 0.47$)
SSGXVIII/AIO, Joensuu et al. 2012 [7, 65][a]	Two arms, open, randomized, multicenter, prospective; imatinib 400 mg daily for 1 versus 3 years	200 (1 year), 200 (3 years)	Primary GIST KIT-positive after radical resection; high risk of relapse (modified NIH classification): tumor size >10 cm *OR* mitotic index >10/50 HPFs *OR* mitotic index >5/50 and tumor size >5 cm *OR* tumor rupture	Significant improvement in RFS with 3-year imatinib therapy as compared with 1-year therapy at median follow-up of 54 months (HR 0.46, 95 % CI 0.32–0.65; $p < 0.0001$); 5-year RFS: 65.6 versus 47.9 %	Significant improvement in OS with 3-year imatinib therapy as compared with 1-year therapy at median follow-up of 54 months (HR 0.45, 95 % CI 0.22–0.89; $p = 0.019$); 5-year OS: 92.0 versus 81.7 %

Table 2 continued

Study	Study design	No. of patients	Major eligibility criteria	Results	
				Primary endpoint	Secondary endpoints
EORTC 62024, Hohenberger at al. 2012 [99]	Two arms, open, randomized, multicenter, prospective; imatinib 400 mg daily for 2 years versus observation	906	Primary GIST KIT-positive after radical resection; intermediate or high risk of relapse (NIH classification): tumor size >5 cm *AND/OR* mitotic index >5/50 HPFs	Time to imatinib failure at relapse (changed from OS)	RFS, OS, safety: results are expected in 2013

ACOSOG American College of Surgeons Oncology Group, *AIO* Arbeitsgemeinschaft Internistische Onkologie, *CI* confidence interval, *EORTC* European Organization for Research and Treatment of Cancer, *HPFs* high-powered fields, *HR* hazard ratio, *KIT* v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog, *NIH* National Institutes of Health, *OS* overall survival, *R0* microscopically radical resection of the tumor, *RFS* recurrence-free survival, *SSG* Scandinavian Sarcoma Group

[a] Studies evaluating adjuvant therapy with imatinib for at least 3 years

More patients discontinued imatinib therapy in the 36-month treatment arm than in the 12-month arm, for reasons other than GIST recurrence (25.8 vs. 12.6 %; $p < 0.001$) [7, 65].

5 Assessment of the Risk of Recurrence after Primary Surgery, and Patient Selection for Extended Adjuvant Imatinib Therapy

Evaluation of the risk factors for recurrence after primary surgery is essential for reliable prognosis, scheduling of follow-up, and identification of patients who may potentially benefit from adjuvant therapy. The main criteria taken into account in a few existing risk stratification systems include the tumor site, size, mitotic index, and tumor rupture; however, the uniform risk criteria remain difficult to determine.

The National Institutes of Health (NIH) consensus criteria formulated in 2001 provided the first evidence-based categorization and a practical scheme for risk assessment in the clinical course of this disease. This risk classification was based on the tumor size and mitotic rate [evaluated per 50 high-powered fields (HPFs)] as the most reliable prognostic factors [66]. This scheme was complemented in 2006 by Miettinen and Lasota from the Armed Forces Institute of Pathology (AFIP), who recognized the significance of the tumor location as an independent prognostic factor in GISTs. They created a new risk assessment scheme (recommended by the NCCN and commonly used) which reflected better prognosis of gastric GISTs compared with intestinal GISTs of the same mitotic index and size [21, 67–70] (Table 3 and Fig. 1). The same prognostic factors were taken into account in the nomogram created by Gold et al. [71], which seems to vaguely outperform the NIH and NCCN–AFIP criteria. Moreover, it has been demonstrated that tumor rupture (either spontaneous or iatrogenic) is an important risk factor, which strongly correlates with the risk of recurrence in GISTs [72, 73]. This observation has led to the development of modified NIH criteria and novel non-linear risk stratification systems, including prognostic contour maps and heat maps, constructed on the basis of the tumor size, site, mitotic index, and incidence of tumor rupture [73–75]. These features may provide even more accurate estimation of the risk of recurrence and are appropriate for individualizing risk stratification for adjuvant therapy in GISTs. Subgroup analysis of the ACOSOG Z9001 trial confirmed that the major clinical benefit of adjuvant therapy was limited to the group of patients at high risk of relapse according to the NCCN–AFIP criteria (an improvement in 2-year RFS from 41 to 77 %; $p < 0.0001$) [76].

In addition to clinicopathological factors, molecular features may also present added value to risk stratification

Table 3 National Comprehensive Cancer Network (NCCN)–Armed Forces Institute of Pathology (AFIP) risk criteria after resection of primary gastrointestinal stromal tumors (GISTs), according to Miettinen and Lasota [9]

Tumor parameters		Primary tumor location and risk of recurrence			
Size	Mitotic index	Stomach	Duodenum	Small intestine	Rectum
≤2 cm	≤5/50 HPFs	0 %	0 %	0 %	0 %
>2 cm, ≤5 cm		Very low (1.9 %)	Low (8.3 %)	Low (4.3 %)	Low (8.5 %)
>5 cm, ≤10 cm		Low (3.6 %)	High (34 %)	Intermediate (24 %)	High (57 %)
>10 cm		Intermediate (12 %)		High (52 %)	
≤2 cm	>5/50 HPFs	Insufficient data	Insufficient data	High (50 %)	High (52–71 %)
>2 cm, ≤5 cm		Intermediate (16 %)	High (50–86 %)	High (73–90 %)	
>5 cm, ≤10 cm		High (55–86 %)			
>10 cm					

HPFs high-powered fields

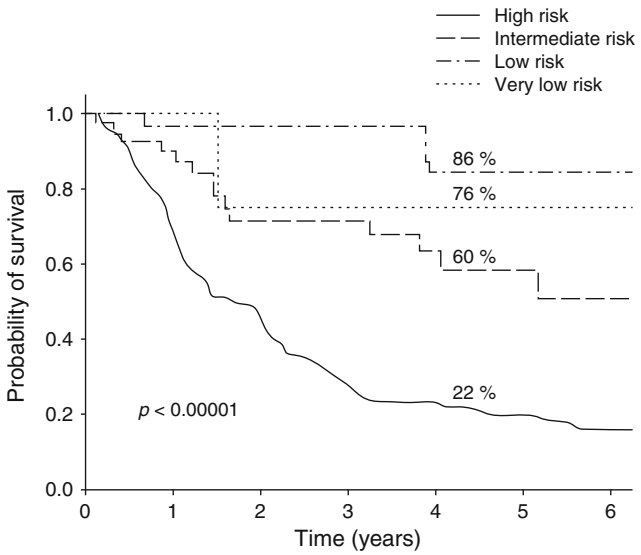

Fig. 1 Recurrence-free survival in small-bowel gastrointestinal stromal tumors (GISTs), according to National Comprehensive Cancer Network (NCCN)–Armed Forces Institute of Pathology (AFIP) risk categories (based on the authors' own data from 659 primary GISTs after radical resection, presented during the European Society of Surgical Oncology conference [100])

of GISTs. However, they have not been included in the present risk assessment guidelines. Several studies have demonstrated better prognosis for patients harboring *KIT* exon 11 point mutations or insertions, as well as *PDGFRA* exon 18 mutations. On the other hand, tumors carrying *KIT* exon 11 deletions (especially involving codons 557 or 558) and *KIT* exon 9 duplications are associated with an aggressive disease course [30, 77–83]. It has also been proposed that genomic complexity, defined by a genomic index determined by array comparative genomic hybridization, may serve as a useful adjunct to the current risk stratification systems, which are often uninformative in the case of intermediate-risk patients [84, 85].

It is worth noting that the updated FDA and EMA approvals for 36 months of imatinib treatment apply to patients who specifically meet the inclusion criteria determined in the SSGXVIII/AIO trial [7, 65]. In that trial, imatinib treatment was initiated within the first 12 weeks after primary surgery. Patients were eligible for the trial if they had KIT-positive GISTs and demonstrated at least one of the following features: longest tumor diameter >10 cm, mitotic index >10/50 HPFs, longest tumor diameter >5 cm and mitotic index >5/50 HPFs, or tumor rupture prior to or at the time of surgery. This classification represents a modified NIH risk-stratification system, complemented with tumor rupture as an independent prognostic factor [75]. Tumor location was excluded from the risk assessment criteria in this study. Gastric GISTs constituted approximately half of the cases in both the 12- and 36-month arms, followed by small-intestine GISTs (37 and 31 % of cases, respectively), and GISTs located in the colon or rectum constituted 8 and 10 % of cases, respectively. In 7 % of patients in each arm, the tumor was in another location or the location was unspecified.

6 Benefit of and Resistance to Adjuvant Imatinib Therapy

The results of the SSGXVIII/AIO trial [65] demonstrated that mutational analysis of GISTs may have predictive value for the clinical response to adjuvant imatinib therapy, similar to data observed in the metastatic setting. From the molecular point of view, resistance to imatinib has its origins in *KIT/PDGFRA* mutational status. Data reported by Joensuu and colleagues [65] showed that patients with *KIT* exon 11 mutations benefit the most from prolonged adjuvant treatment. Similar data were shown for patients treated in the ACOSOG Z9001 trial [86]; the 2-year RFS rate was 91 % for patients treated with adjuvant imatinib

harboring *KIT* exon 11 mutations, as compared with 65 % in a group of patients with the same genotype receiving placebo ($p < 0.0001$).

On the other hand, primary imatinib resistance in the adjuvant setting has been demonstrated especially in cases carrying a *PDGFRA* exon 18 p.D842V mutation, presumably because of the structural alterations at the imatinib binding site. This mutation is detected in approximately 10 % of operable GISTs [75, 87], especially in tumors originating from the stomach (exceeding 20 % of cases in this location) [30]. Adjuvant imatinib should not be recommended in cases of GISTs harboring a *PDGFRA* exon 18 p.D842V mutation. In the ACOSOG Z9001 trial [86], adjuvant imatinib therapy had no positive impact on RFS in this subgroup of patients.

Interestingly, it has been demonstrated that patients with advanced GISTs harboring mutations in *KIT* exon 9 may benefit from an imatinib dose increase to 800 mg daily [62]. This indicates that patients with this mutation may be underdosed when receiving 400 mg of imatinib daily, but it has never been examined in any clinical trial in the adjuvant setting. In wild-type GISTs, the tumor size and mitotic index poorly predict clinical outcome; therefore, current risk stratification systems seem to be inapplicable in this subgroup of patients [50, 51]. Moreover, wild-type GISTs present a limited response to imatinib treatment, in comparison with GISTs carrying imatinib-sensitive mutations. Adjuvant imatinib efficacy in *KIT* exon 9 mutants and wild-type GISTs warrants further study; however, the numbers of patients in these subgroups are usually small, and so statistical significance is difficult to reach when these categories are analyzed [86]. Nevertheless, *KIT* and *PDGFRA* genotyping in GISTs should be performed routinely in the adjuvant setting, since it may help to tailor the treatment to patients who are more likely to respond to imatinib therapy, or to exclude patients with imatinib-resistance mutations [86, 88].

In the SSGXVIII/AIO trial, patients were monitored for their response to imatinib with contrast-enhanced computed tomography or magnetic resonance imaging at 6-month intervals for the first 7 years and annually thereafter. An initial staging examination was performed within 28 days before the introduction of imatinib treatment. Blood biochemistry and cell counts were performed at 1- to 3-month intervals in the course of the treatment [65]. GIST relapse is usually observed at the highest frequency within the first 2 years after completion of adjuvant treatment; therefore, regular imaging in this period is especially important for early detection of recurrence [64, 76]. The majority of patients who develop GIST recurrence after completion of adjuvant imatinib respond to an imatinib rechallenge regardless of the prior treatment duration [64]. On the basis of the clinical behavior of advanced GISTs, it may be anticipated that in patients who relapse during adjuvant treatment or within the first few weeks after completion of adjuvant treatment, an increased dose of imatinib or introduction of another tyrosine kinase inhibitor, such as sunitinib, may be beneficial because these cases are probably primarily imatinib resistant. However, no clinical trial has addressed this hypothesis as yet [64]. Generally, only a few patients in the SSGXVIII/AIO trial developed GIST recurrence during imatinib treatment (2 % of patients in the 12-month arm and 6 % of patients in the 36-month arm). This suggests that acquired resistance to adjuvant imatinib (related mainly to occurrence of secondary *KIT/PDGFRA* mutations) is infrequent in this patient population [7, 65].

The optimal duration of imatinib therapy is not yet known. We still do not know if adjuvant imatinib therapy can cure a patient by preventing relapse or can only delay it. In the metastatic setting, interruption of imatinib therapy has been associated with disease relapse at a median of 6 months after stopping imatinib after 1, 3, or 5 years of treatment [89, 90]. The significant improvement in OS associated with 3 years versus 1 year of adjuvant imatinib in the SSGXVIII/AIO trial [7, 65] was based on the limited number of deaths that occurred at median follow-up of 54 months, and so longer follow-up is needed to confirm the OS advantage related to 3-year adjuvant imatinib therapy.

7 Future of Adjuvant Imatinib Therapy

There are still several unresolved issues concerning future use of adjuvant imatinib in GISTs. In the coming years, adjuvant imatinib treatment for at least 3 years will be standard therapy in high-risk GIST patients harboring sensitive mutations. In intermediate-risk patients, adjuvant imatinib should be considered, provided there is better characterization of individual prognostic features. The role of adjuvant imatinib therapy in patients with wild-type GISTs or *KIT* exon 9 mutations should be better defined, and the appropriate initial dose of imatinib—400 or 800 mg daily in patients with *KIT* exon 9 mutants—must be established. The optimal duration of adjuvant imatinib therapy beyond 3 years requires further investigation and should preferably be determined on the basis of randomized controlled trials. Furthermore, the optimal follow-up schedule after discontinuation of the therapy is not well established. The only issue that seems to be incontestable in the immediate future is the necessity for genotyping of every primary GIST considered for adjuvant therapy [91].

8 Conclusions

Despite the striking efficacy of imatinib, recurrent or metastatic GIST is still not a curable disease. This implies

that prevention of disease recurrence following surgical resection of the primary tumor is the key to further improvement of the clinical outcomes of patients affected by GISTs. Three years of adjuvant imatinib treatment, as opposed to 1 year of treatment, significantly reduced the risk of recurrence and improved OS in patients with KIT-positive GISTs at high risk of recurrence after surgery [7]. Currently, 3 years of adjuvant treatment for patients at high risk of recurrence may be considered as a standard of care. However, it is not clear whether patients who are classified as intermediate risk should be treated with adjuvant imatinib. Results from several phase II studies support the idea that at least 2 years of adjuvant imatinib treatment is beneficial for intermediate-risk GISTs (especially those harboring *KIT* exon 11 mutations) and may be considered in this subgroup of patients [92–97]. On the other hand, patients with very low-risk or low-risk tumors are likely to be cured by surgery alone and should not receive adjuvant imatinib.

Beyond risk assessment for proper selection of patients for adjuvant imatinib therapy, mutational status also has a predictive value for clinical response to the therapy. It may help to tailor the treatment to patients carrying more sensitive mutations, such as *KIT* exon 11 mutations, or to exclude patients with imatinib-resistance mutations, such as a *PDGFRA* p.D842V mutation. Thus, *KIT* and *PDGFRA* genotyping of patients with GISTs is obligatory in the adjuvant setting [86, 88].

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