Adjuvant and Neoadjuvant Treatment

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Abstract

Although surgical complete resection remains the only curative intervention for GIST, more than 40% of completely resected GISTs, especially those expressing high-risk features, such as large tumors or tumors with a high mitotic rate, are likely to develop recurrence with distant metastasis. In the past two decades, tyrosine kinase inhibitors were introduced for the treatment of GIST, and imatinib greatly prolonged the survival of metastatic or unresectable disease. This efficacy has encouraged the use of imatinib in perioperative settings; however, the staging system (risk estimation) is immature, and thus which patients need adjuvant or neoadjuvant therapy the most is unclear. A recent phase III trial revealed that adjuvant imatinib improves the recurrence-free survival of high-risk GISTs, but the optimum duration of imatinib and the impact on the overall survival remain controversial. Neoadjuvant treatment is a promising strategy for marginally resectable GISTs, but the prospective comparison of adjuvant and neoadjuvant therapy for such patients has not been performed. The further accumulation of evidence and the establishment of universal risk estimation and prevalence of genotyping are necessary in order to facilitate the perioperative treatment of GIST.

Keywords

Gastrointestinal stromal tumor · Adjuvant treatment · Neoadjuvant treatment
Imatinib

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10.1 Introduction

Gastrointestinal stromal tumors (GISTs) are the most common sarcomas of the gastrointestinal tract. All GISTs are potentially malignant, but their potential ranges from indolent to highly aggressive. Although most localized GISTs are indicative for primary surgery and are completely resected as planned, surgery alone may cause relapse in 40–50% of completely resected GISTs [1, 2].

Approximately, 90% of GISTs harbor gain-of-function mutations in either the KIT or platelet-derived growth factor receptor alpha (PDGFRA) genes [3] that have been identified as driver genes of GIST [4–6]. These mutations are basically mutually exclusive, and different mutations do not exist simultaneously in the same tumor. It can be said that GISTs are a genetically simple and relatively homogeneous disease, except for the so-called wild-type (both KIT/PDGFRA mutation-negative) GISTs, which include several minor mutations, such as NF1 or BRAF. This genetic homogeneity is one of the largest advantages in treating GISTs using tyrosine kinase inhibitors (TKIs).

At present, three TKIs, imatinib, sunitinib, and regorafenib, have been approved as first-, second-, and third-line therapies for the treatment of patients with KIT-positive GISTs. It has been reported that 45–52% of patients with metastatic GIST responded to first-line imatinib with acceptable toxicities [7, 8]. Although surgery remains the mainstay treatment for easily resectable GISTs, surgery alone for locally advanced and/or marginally resectable GISTs is not satisfactory, especially in this era of TKIs.

This review will discuss the significance of the perioperative use of imatinib for localized GISTs.

10.2 Overview

The ultimate goal of perioperative imatinib is to cure locally advanced and/or marginally resectable GISTs in which no residual tumor (R0) is difficult to achieve by surgery alone or in which recurrence may develop even after R0 surgery. As routine lymphadenectomy does not contribute to the outcome of the treatment of GIST, it is also desirable to preserve the organ function and avoid extended surgery as much as possible. However, evidence supporting perioperative adjuvant therapy is insufficient at present, and optimum candidates remain unclear.

10.2.1 Who Benefits from Perioperative Imatinib?

Perioperative therapy includes either or both preoperative or postoperative intervention. Generally, TNM staging is not adapted to the preoperative evaluation of GIST because GISTs rarely metastasize to lymph nodes. The mitotic count is one of the most important factors in evaluating the risk of recurrence; however, its evaluation from a biopsy is not reliable due to the heterogeneity within these tumors [9].

Accordingly, a treatment decision is made by not only pathological findings but also by considering the clinically specific features of GIST, such as tumor rupture.

10.2.1.1 Large GISTs

Patients with GISTs rarely complain of symptoms associated with bowel obstruction because large GISTs usually develop expansively and extraluminally. Almost two-thirds of patients with GIST had tumors over 5 cm in size at the diagnosis, and some tumors grew to be as large as 40 cm [1]. The tumor volume doubling time on computed tomography (CT) was reported to be almost 1 year [10], which is significantly shorter than schwannoma (doubling time: 4.6 years). This rapid growth without symptoms may allow these tumors to grow large, making complete resection difficult.

In general, the complete resection rates for GISTs without metastasis are reported to be around 80% by surgery alone [2]. Even after the tumor is completely resected, large GISTs still have considerably high risks of recurrence. The 5-year recurrence-free survival (RFS) rate of large GIST (>10 cm) is 35–50% if the patient does not receive adjuvant therapy [1]. Neoadjuvant treatment is a promising strategy for large GISTs with low complete resection rates and a high risk of rupture. In addition, in tumors >10 cm in size, downstaging (to a lower-risk category) does not occur only by pathological modification from neoadjuvant treatment because "size >10 cm" is itself a definitive factor for the high-risk category.

10.2.1.2 Tumors with Rupture or at Risk of Rupture

At tumor rupture, tumor cells spill and become disseminated in the abdominal cavity. Therefore, macroscopic complete resection of ruptured GIST is treated as R1 surgery, not as R0. The prognosis of ruptured GIST is poor; the 5-year RFS rate of ruptured GIST is approximately 20% if the patient does not receive adjuvant therapy [1]. Ruptured GISTs have a high risk for peritoneal recurrence in theory, but more exactly, preoperative spontaneous rupture and intraoperative rupture associated with surgical manipulation should be differently classified because the intraoperatively disseminated tumor cells could be washed and collected before they are implanted in the peritoneum.

Tumor rupture occurs in 5–7% of GISTs [1, 11] and does not always happen to large GISTs. In a study of 23 patients with ruptured GISTs [12], the median tumor size of the ruptured lesions was 8 cm (range 4–28 cm). The association between the tumor growth pattern and the occurrence of peritoneal metastasis was examined in another study. It was reported that peritoneal metastasis more frequently occurred in extraluminal tumors (50%: 15/30) than in intraluminal tumors (10%: 1/10) [13]. Although whether or not tumor shrinkage due to imatinib prevents spontaneous tumor rupture is unclear, tumor rupture during imatinib treatment in neoadjuvant setting has not been reported.

10.2.1.3 Difficult-to-Resect Anatomical Location

GISTs can arise from all digestive tracts, with frequencies of 5% in esophagus, 70% in stomach, 20% in small intestine, and 5% in colon and rectum. Among these sites,

the esophagus, duodenum, and rectum are located in the narrow spaces of the mediastinum, retroperitoneum, and pelvis, respectively. Tumors occurring in these sites are difficult to resect and likely to rupture during surgery, and preserving the organ function is also difficult. Tumor shrinkage may improve the surgical difficulty and prevent intraoperative tumor rupture, and it may also help avoid highly invasive surgery, e.g., pancreaticoduodenectomy (PD) in duodenal GIST and rectal amputation in rectal GIST. It was reported that 30–40% of patients with duodenal GIST underwent PD, and the rest underwent conservative surgery, but the surgical approach did not affect the risk of recurrence [14, 15].

10.2.1.4 "High-Risk" GISTs

The term "high-risk" refers to patients who have been clinically or pathologically evaluated as being at high risk for recurrence after macroscopic complete surgery (R0 or R1). Several risk factors for recurrence in GIST were identified, and which of these is the strongest prognosticator has been the subject of some debate. Four factors are now widely accepted as predictive factors of recurrence: the mitotic count, tumor size, tumor site, and rupture. Originally, the risk for each tumor was evaluated by the combination of two factors (mitotic count and tumor size) under the National Institute of Health (NIH) consensus criteria [16]. Thereafter, primary site was added in the Armed Forces Institute of Pathology (AFIP) criteria [17], and tumor rupture was added in the modified NIH consensus criteria [18]. The 5-year RFS rate of high-risk GISTs under the modified NIH consensus criteria is around 40% if the patient does not receive adjuvant therapy [1]. Patients evaluated as high-risk before operation are candidates for both adjuvant and neoadjuvant therapy (Fig. 10.1).

10.2.1.5 Imatinib-Sensitive GIST

Tumor genotyping is a predictive marker of the efficacy of imatinib, and most of the mutational subtypes in GIST respond well to imatinib. Several subtypes (PDGFRA exon18 D842V, KIT exon17 D816V, and both KIT/PDGFRA wild-type) are known to have no or an inferior response to imatinib [19]. KIT exon9 has a higher response to high-dose (800 mg/day) than to low-dose (400 mg/day) imatinib [20], but high-dose imatinib is not approved for GIST in Japan. Therefore, patients with such imatinib-resistant mutations are at risk of receiving ineffective treatment for a long time if they receive adjuvant treatment and may miss the chance to undergo surgery due to tumor progression if they receive neoadjuvant treatment.

10.3 Adjuvant Therapy

In the setting of advanced and metastatic GISTs, a longer survival has been shown to be correlated more closely with smaller tumors in the treatment of imatinib than with larger tumors. If imatinib responds in reverse proportion to the tumor size, then microscopic metastasis would be the best target of imatinib therapy in theory. However, the standard method for detecting microscopic metastasis has not yet been established.

The target patients who warrant adjuvant imatinib are currently being discussed in terms of the tumor stage (risk estimation) and sensitivity to imatinib (genotyping). As with other sarcoma tumors, GISTs are proposed to obey a classification system defined by tumor size and pathological grade. This is called "risk classification" or "risk criteria." Under the original NIH consensus criteria, the mitotic count per 50 high-power fields (HPF) was used as the index for the pathological grade. The survival curves of each risk group classified by the NIH consensus criteria are clearly separated, but some problems may arise when the original NIH consensus criteria is used for selecting optimum patients who would benefit from adjuvant therapy with imatinib.

The first problem is the issue of discontinuity of risk. Since both the tumor size and mitotic count are continuous variables, the risk of a tumor is likely to be evaluated differently if there is even a small difference in the tumor size or mitotic count around the cut-off value. For example, a 5.0-cm GIST with a mitotic count of 5/50 HPF is evaluated as a low-risk lesion, but a 5.1-cm GIST with a mitotic count of 6/50HPF is evaluated as a high-risk lesion. For such marginal cases, the supplemental usage of another tool is recommended. Contour maps for predicting the 10-year risk of recurrence after surgery are useful for reducing this gap in risk estimation [1].

The second problem is the issue of the reliability and reproducibility of the mitotic count. The criteria for identifying mitosis are different between pathologists [21]. Indeed, the mitotic count is reported to differ between local and central pathologists. In general, local pathologists tend to count mitosis higher than central pathologists. The field-of-view of the eyepiece for the microscope should also be noted. The field-of-view of more recently manufactured eyepieces is almost twice that of older eyepieces. The European Society for Medical Oncology (ESMO) guideline recommends that the mitotic count be expressed as the number in a 5-mm^2 area, which is equivalent to 50 HPFs with a conventional eyepiece [22]. Other methods like the Ki-67 labeling index have also been considered for use in place of the mitotic count, although the mitotic count has yet to be replaced formally.

10.3.1 Clinical Trials

To date, two phase I and three phase II trials of adjuvant therapy have been conducted. The results have already been published, excluding one phase II trial (PERSIST5). All of these trials have targeted "high-risk" GISTs, but the definition of high-risk varied among trials (Table 10.1). Whether or not adjuvant therapy should target intermediate-risk patients under the NIH consensus criteria as well as high-risk patients is still controversial. No trial has yet mandated genotyping before registration.

10.3.1.1 ACOSOG Z9000

Based on the successful results of imatinib for advanced or metastatic GIST, the first phase II trial, ACOSOG Z9000, was conducted to test the efficacy and safety of adjuvant imatinib [23]. A total of 106 patients were accrued, and the patients were

Table 10.1 Differences of eligibility criteria in phase II/III trial of adjuvant imatinib

Trial	Phase	Intervention	Inclusion criteria (tumor)
ACOSOG Z9000	II	Imatinib 400 mg/day for 12M	Size >10 cm, tumor rupture, peritoneal implants (up to 4)
PERCIST5	II	Imatinib 400 mg/day for 60M	Primary GIST (any site): ≥ 2 cm and a mitotic rate of ≥ 5/50 HPFs Non-gastric primary GIST: ≥ 5 cm
ACOSOG Z9001	III	Placebo vs Imatinib 400 mg/day for 12M	Size ≥3 cm
SSG-XVIII	III	Imatinib 400 mg/day for 12M vs for 36M	High risk at NIH consensus criteria or tumor rupture
EORTC62024	III	Placebo vs Imatinib 400 mg/day for 24M	High and intermediate risk at NIH consensus criteria

prescribed imatinib 400 mg/day for 1 year. The primary endpoint was the overall survival (OS), and adjuvant imatinib was expected to prolong the OS from 35% (historical control) to 50%. The secondary endpoints were the RFS and patient safety. The 5-year OS rate was 83%, which was more favorable than expected. The 1-, 3-, and 5-year RFS rates were 96%, 60%, and 40%. Although adjuvant imatinib prevented recurrence in most cases, the effect did not continue after the termination of treatment. The median RFS of the patients with KIT exon11 was more favorable than that of those with KIT exon9 (42 vs. 19 months) but poorer than that of those with PDGFRA and wild-type. The result was consistent with the data reported in a previous trial of advanced and metastatic settings. The finding that none of the patients with KIT exon9 recurred in the first year indicated that imatinib 400 mg/day is effective for the prevention of recurrence even in patients with KIT exon9. Although high-dose (800 mg/day) imatinib was associated with a longer survival among patients with the KIT exon9 mutation in the advanced and metastatic settings, whether or not high-dose imatinib has a more favorable effect than low-dose administration in an adjuvant setting is unclear.

10.3.1.2 ACOSOG Z9001

The ACOSOG Z9001 is a randomized phase III, double-blind trial [24]. A total of 713 patients who had a histological diagnosis of primary GIST measuring ≥3 cm in size were randomly assigned to receive 1 year of adjuvant imatinib at a dose of 400 mg/day or 1 year of placebo. The original primary endpoint was the OS, which was then changed to the RFS because it gradually became clear that the event (death) rarely occurred if patients received imatinib therapy after recurrence. The trial was stopped early following the planned interim analysis because significantly fewer patients experienced recurrence with the drug than with the placebo. These findings indicated that 1-year imatinib did indeed significantly improve the RFS compared with placebo, with an RFS rate at 1 year of 98% in the imatinib group and 83% in the placebo group and a hazard ratio of 0.35 (95% confidence interval: 0.22–0.53). In risk factor analysis, a large tumor size (>10 cm), high mitotic count (≥10/50 HPF), and small bowel origin were independent risk factors for a worse

RFS in imatinib arm as well as placebo arm [25]. Strangely, the hazard ratio of large tumor size (>10 cm) against reference (size <5 cm) in imatinib arm was 6.51, and it was rather increased as compared with the hazard ratio in placebo arm (3.25). This result might suggest that the benefit of adjuvant imatinib was smaller in large GIST than in small GIST, and another strategy should be considered for large GISTs. The RFS for patients with KIT exon11 was longer in the imatinib group than in the placebo group. The same trend was not observed in patients with KIT exon9 and wild-type tumors.

10.3.1.3 EORTC62024

The EORTC62024 trial was a randomized phase III trial comparing 2 years of adjuvant imatinib to observation alone [26]. The original primary endpoint was the OS but was changed to imatinib failure-free survival (IFFS) in 2009, given the recent development of post-imatinib treatment and improvement in the prognosis. The IFFS was defined as the time to death or starting another TKI. A total of 908 patients were randomly assigned to adjuvant imatinib or observation. The patients who had high-risk tumors (i.e., mitotic count >10/50 HPF and tumor diameter over 10 cm, or mitotic count >5/50 HPF and a tumor diameter of over 5 cm) or intermediate-risk tumors (i.e., tumor size ≤5 cm and mitotic count 6/50 to 10/50 HPF, or tumor size >5 to 10 cm and mitotic count ≤5/50 HPF) were eligible. Briefly, there was a significant difference in the RFS (84% in the imatinib arm and 64% in the observation arm at 3 years, log-rank $p < 0.001$), but no significant difference in the 5-year IFFS (87% in the imatinib arm and 84% in the observation arm, hazard ratio [HR]: 0.79, 98.5% CI of 0.50–1.25). When the analysis of the 5-year IFFS was limited only to the high-risk subcategory, there was a trend favoring the imatinib arm, but it was not statistically significant (79% in the imatinib arm and 73% in the observation arm, $p = 0.087$).

10.3.1.4 SSG XVIII

A phase III randomized controlled trial conducted by the Scandinavian Sarcoma Group (SSG) compared 36 months vs. 12 months of adjuvant imatinib after the resection of high-risk GIST [27]. The eligibility criteria of this study were one of the following: mitotic count >10/50 HPF and tumor diameter >10 cm, mitotic count >5/50 HPF and tumor diameter >5 cm, or tumor rupture. The tumor site was not considered for the high-risk definition. A total of 400 patients were allocated to each group. A central pathological review confirmed that 15 of 397 patients (4%) were not GIST. At a median follow-up of 54 months, the 5-year RFS was significantly longer in the 36-month group than in the 12-month group (65.6% vs. 47.9%, HR = 0.46 with 95% CI of 0.32–0.65, $P < 0.001$). Furthermore, the 5-year OS was also significantly longer in the 36-month group than in the 12-month group (92.0% vs. 81.7%, HR = 0.45 with 95% CI, 0.22–0.89; $P = 0.02$). The second planned analysis at a median follow-up of 90 months revealed that the survival benefit persisted with a longer 5-year RFS (71.1% vs. 52.3%) and 5-year OS (91.9% vs. 85.3%) in the 36-month group compared with the 12-month group [28]. Adverse events occurred more frequently in the 36-month group than in the 12-month group,

but the grade was generally mild. The most common event in the 36-month group was anemia (80.3%), followed by periorbital edema (74.2%) and diarrhea (54%). Adverse events were associated with treatment discontinuation in 13.6% of the 36-month group and 7.5% of the 12-month group.

10.3.2 Patient Selection

There is rough consensus among experts that risk estimation tools should be used for optimum patient selection for adjuvant therapy; however, which tool should be used and what cut-off should be selected remain unclear. Joensuu et al. [1] compared the prognostic accuracy of risk estimation tools using a receiver operating characteristic (ROC) curve and found in estimating the 10-year recurrence risk that the best predictor of recurrence was a nonlinear model that included tumor rupture data. The areas under the curve (AUCs) of the nonlinear model including rupture, the NIH consensus criteria, AFIP criteria, and modified NIH consensus criteria were 0.88, 0.79, 0.82, and 0.78, respectively. These analyses suggested that it is better to use a tool that includes tumor rupture when adjuvant therapy is considered, although the definition of tumor rupture remains unclear. The indication for adjuvant therapy should be carefully considered for patients who suffer from tumor rupture as a single high-risk factor.

As for the cut-off of risk category, that for high-risk is definite, but that for intermediate-risk is controversial. In the EORTC62024 study, which included intermediate-risk patients in their eligibility criteria, there were no statistically significant differences in the RFS between the high- and intermediate-risk subgroups ($p = 0.111$). At present, data are insufficient to determine whether or not patients with intermediate risk benefit from adjuvant imatinib. We should at least not include all patients with intermediate risk and instead screen patients or reevaluate individual risk using several risk estimation tools (please refer to Chap. 5).

10.3.3 Optimum Duration of Adjuvant Therapy

The ideal goal of adjuvant therapy is the complete elimination of minimal residual disease and cure. Generally, the duration of adjuvant therapy is about 6 months to 1 year in gastrointestinal cancers, such as gastric cancer or colorectal cancer. GISTs also occur from the digestive tract, but the duration of adjuvant therapy is considered differently from gastrointestinal cancers because imatinib acts as a cytostatic agent rather than a cytotoxic agent.

Whether the long-term treatment of imatinib can eradicate microscopic disease or simply delays recurrence is controversial. Two conflicting results have been found concerning the effect of adjuvant imatinib. In the SSG XVIII trial, a longer treatment (3 years) improved not only the RFS but also the OS compared with a shorter treatment (1 year). In contrast, in the EORTC62024 study, 2 years of adjuvant imatinib helped prolong the RFS but did not prolong the OS compared to observation alone.

Determining which evidence is more appropriate to extrapolate to clinical practice is difficult because of several differences between the two studies. For example, patients with intermediate risk were included in the EORTC study but not in the Scandinavian study. In addition, the standard arm was observation alone in the EORTC study but 1-year imatinib in the Scandinavian study. Furthermore, the duration of adjuvant imatinib in the test arm was also different, being 2 years in the EORTC study and 3 years in the Scandinavian study. We also have little information on post-imatinib treatment, which may have a large impact on the OS.

Despite these differences, a longer duration of imatinib was associated with a longer RFS in both studies. The effect of further long duration of imatinib (5 years) is currently being evaluated in the PERSIST5 study.

In summary, 2–3 years of adjuvant imatinib is acceptable and can be recommended for maintaining a long RFS. The follow-up and post-imatinib therapy as well as the duration of adjuvant therapy are important for prolonging the OS.

10.3.4 Follow-Up After Stopping Adjuvant Therapy

As adjuvant imatinib reduces the risk of recurrence after surgery, the patients who underwent adjuvant imatinib might as well follow the modified examination schedule of high-risk GIST. During the adjuvant period, the risk of recurrence is small, unless the patient has a tumor with an imatinib-resistant genotype. The ESMO guideline describes a routine follow-up schedule for patients with GIST who undergo adjuvant therapy, and a follow-up example with an imaging interval of every 3–6 months during adjuvant therapy is mentioned [22]. Patients with an unavailable tumor genotype are recommended to receive a checkup every 3 months. After discontinuation of adjuvant imatinib, the risk of recurrence is likely to increase. In the SSG XVIII trial, recurrence frequently occurred after stopping adjuvant imatinib in both the 1-year and 3-year arms. Therefore, patients who undergo adjuvant imatinib should receive follow-up with a short interval including imaging examinations every 3 months for 2 years after stopping adjuvant therapy. Thereafter, once in every 6 months for several years is a feasible interval for imaging examinations.

10.4 Neoadjuvant Therapy

Complete surgical resection is the only curative intervention for GIST; however, the resectability is marginal when the tumor has at least one of the following: large size, origin at a difficult-to-resect anatomical location, or risk of rupture. The success of imatinib in the advanced and metastatic settings has supported its use in the neoadjuvant setting for locally advanced or marginally resectable GISTs. In particular, the high response rate and tumor-associated shrinkage suggested benefits with this agent in preoperative treatment.

In the phase II study of imatinib 400 mg/day for unresectable or metastatic GIST, the overall response rate was 68.5% (complete response [CR]: 0%, and partial response [PR]: 68.5%) in the lower-dose group [29]. In another retrospective study, imatinib reduced the tumor diameter and tumor volume by 43% and 83% at the timing of best response [30]. Volume reduction may help prevent intraoperative tumor rupture, especially in the narrow regions of the mediastinum, retroperitoneum, and pelvis. The potential advantages of neoadjuvant imatinib are facilitating complete resection and preventing extended surgery as well as recurrence after surgery. In addition, evaluating the response to preoperative treatment by imaging provides useful information for postoperative therapy in which no target lesion is available. However, CR is associated with a loss of pathological information. RECIST CR is very rare in GIST, but we sometimes experience cases in which tumor cells are almost completely absent and no mitosis is observed. As the risk estimation of GIST largely depends on pathological findings, it then becomes difficult to evaluate the risk of recurrence correctly in such cases. Information on the genotype is also likely to be lost unless the genotype has already been analyzed using biopsy tissue.

10.4.1 Clinical Trials

At present, the results of two phase II studies of neoadjuvant imatinib for GIST are available (Table 10.2). The results of another trial (APOLLON study) remain unpublished.

10.4.1.1 RTOG0132

The radiation therapy oncology group (RTOG) 0132 was a prospective phase II study to evaluate the efficacy and safety of neoadjuvant imatinib [31]. The initial dose of imatinib was 600 mg/day. Patients with primary GIST (size ≥5 cm) or recurrent/metastatic tumor (≥2 cm) were eligible. The clinical endpoints were the OS, PFS, time to progression (TTP), response (RECIST), toxicity, and surgical complications. A total of 63 patients (30 primary and 22 metastatic) were ultimately enrolled in the study and received preoperative imatinib therapy for 8–12 weeks and postoperative imatinib for 2 years. Imatinib was stopped on the day before surgery and resumed as soon as possible postoperatively.

Table 10.2 Efficacy of neoadjuvant study

	Phase	Intervention	R0 resection rate	Survival
RTOG0132	II	Imatinib 600 mg/day for 8–12W	77% (primary disease group)	2-year OS rate: 93%
				2-year PFS rate: 83%
Asian trial	II	Imatinib 400 mg/day for 6–9M	91%	2-year OS rate: 98%
				2-year RFS rate: 89%

In the primary tumor group, tumors mildly responded to preoperative imatinib (PR in 7% and stable disease in 83% by RECIST), with no cases of CR or progressive disease during the neoadjuvant period. In contrast, 36 of 44 (81.8%) patients had a complete or partial metabolic response at 1 week on fluorodeoxyglucose-positron emission tomography (FDG-PET) [32]. The mean SUVmax decreased from 14.2 (baseline) to 5.5 (at 1 week). There was one anastomotic disruption. An updated result at a median follow-up of 5.1 years revealed the 5-year PFS and 5-year OS of all patients to be 46.1% and 73.6%, respectively. A high proportion of patients experienced disease progression after termination of 2-year postoperative imatinib therapy [33].

10.4.1.2 Asian Phase II for Large Gastric GIST

An Asian multinational phase II study for patients with gastric GISTs ≥10 cm was conducted to investigate the efficacy and safety of neoadjuvant imatinib [34]. The sample size was calculated based on the hypothesis that neoadjuvant imatinib would improve the R0 resection rate from 70% (historical control) to 85%. The primary endpoint was the R0 resection rate. A total of 56 patients were enrolled in this study and received neoadjuvant imatinib (400 mg/day) for 6–9 months. Neoadjuvant imatinib for ≥6 months was completed in 46 patients. The response rate by RECIST was 62% (95% CI, 48–75%), and median shrinkage rate was 35.4% (range, 0.0–87.0%) (Fig. 10.1). Interestingly, two patients with wild-type GIST responded to neoadjuvant imatinib with rather high shrinkage rate (40.8% and 50.5%). Toxicities were generally mild and there were no treatment-related deaths. The R0 resection rate was 91% (48/53; 95% CI, 79–97%), and organ preservation was achieved in 42 of 48 patients with R0 resection. The 2-year overall and progression-free survival rates were 98% and 89% at a median follow-up time of 32 months.

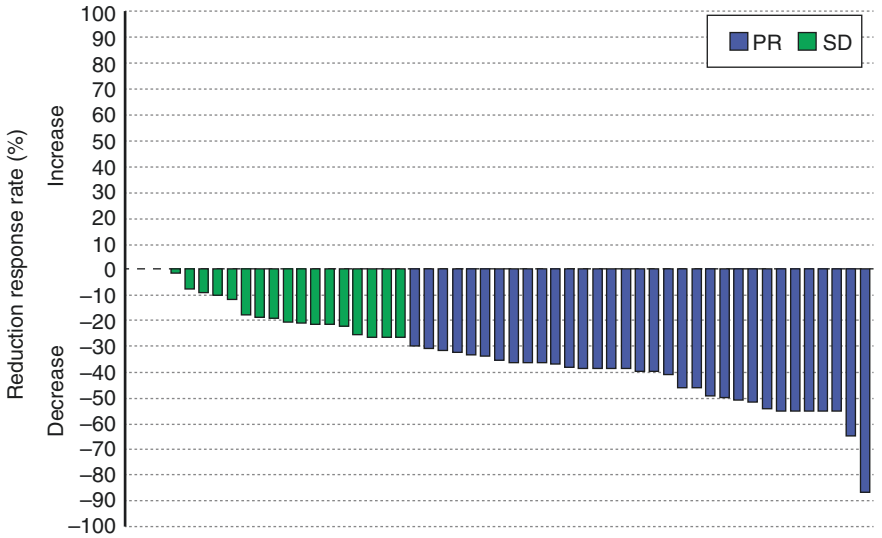

Fig. 10.1 Waterfall plot of tumor shrinkage after neoadjuvant imatinib in Asian phase II study [34]

10.4.2 Duration of Imatinib in Neoadjuvant Therapy

From the perspective of surgical difficulty, it is preferable that tumors be as small as possible, so the preoperative duration of imatinib should be set to reduce the tumor size as much as possible in the neoadjuvant setting. However, the time to best response differs among patients. In the B2222 randomized phase II trial, the median time to response was 2.7 months (range 0.8–39 months), and the time to 75% achieving response was 5.3 months [29]. The median PFS was 24 months (95% CI: 17–30 months). In another phase III study (EORTC62005) in the metastatic setting, the median time to best response was 107 days (interquartile range [IQR]: 58–172 days) [8].

Also in a neoadjuvant setting, the radiologic assessment of the best and plateau response has been reported. In a retrospective study, 20 patients underwent neoadjuvant imatinib with a median treatment duration of 32 weeks. The median time to earliest PR was 16 weeks (IQR 7–26 weeks), and the median time to best response was 28 weeks (IQR18–37 weeks). The time to plateau response was 34 weeks (IQR 24–41 weeks). The tumor size and location did not correlate with the time to best response. Indeed, a short duration of treatment was not effective in the RTOG0132 study. The PR rate was only 7%, and 32% of all nonmetastatic group were unable to achieve complete resection. In contrast, a longer duration was associated with a high R0 resection rate (91%) in the Asian phase II study.

From these data, approximately 6 months (up to 1 year) is reasonable and feasible for achieving adequate tumor shrinkage. Further treatment may increase the risk of imatinib resistance. Imatinib can be continued up to the day before surgery if there is no sign of intestinal edema or severe hematological toxicity. Regarding the timing of starting imatinib after surgery, it is recommended that treatment be started as soon as possible when the patient can take food orally. A consensus-based recommendation supports a total of 3 years of adjuvant imatinib (including preoperative period) based on the results of SSG XVIII.

10.4.3 Operative Procedure

The imatinib plasma trough level has been reported to be associated with the survival in the treatment of GIST, and it was lower in patients with major gastrectomy (942 ± 330 ng/mL) than in those without major gastrectomy (1393 ± 659 ng/mL) [35]. Furthermore, major gastrectomy was found to be an independent risk factor of a lower trough level of plasma imatinib [36]. Therefore, organ preservation is important, especially in patients scheduled to receive postoperative imatinib therapy. Neoadjuvant imatinib is expected to help preserve the organ function through tumor shrinkage.

10.5 Future Directions

No technique has yet been developed to identify microscopic minimal metastasis of GIST. Therefore, no alternative method has been proposed for selecting the best patients to receive adjuvant therapy other than predicting patients who are at a significantly high risk for recurrence. Recently, free-circulating DNA (fcDNA), which is probably released by apoptotic or necrotic tumor cells, has been reported to be a promising marker in patients with tumors and suggests the existence of minimal metastasis or minimal residual disease after curative surgery. In the study of fcDNA in GIST, it was reported that a low level of fcDNA carrying mutations for KIT or PDGFRA was detected in 35% (6/17) of postsurgical patients who had a high or intermediate risk for recurrence [37]. Although the number of patients in the study was too small to draw any hard conclusions and the association between the risk of recurrence and positivity of fcDNA is still unclear, these findings suggest that the detection of fcDNA might be useful for identifying those patients who will most benefit from postoperative adjuvant therapy in the future.

Which patients will most benefit from adjuvant or neoadjuvant therapy remains unclear, and the indication of adjuvant therapy partially overlaps with that of neoadjuvant therapy. When a tumor is larger than 10 cm, the neoadjuvant approach is preferable, irrespective of tumor location, as such tumors are likely to rupture and invade other organs. When the tumor size is 5–10 cm, upfront surgery is recommended, because the recurrence risk should be precisely estimated before the pathological findings are degenerated by imatinib. However, the Japanese guideline states that tumors larger than 5 cm are not suitable for laparoscopic resection. I therefore hypothesize that the risk of intraoperative rupture may be decreased if the tumor size can be reduced to <5 cm. As the median tumor shrinkage rate is reported to be around 40% by neoadjuvant imatinib for 6 months, tumors up to 8 cm in size should decrease to <5 cm with upfront imatinib, in theory. I speculate that GISTs larger than 5 cm, but smaller than 8 cm, are future candidates for clinical trials to verify the efficacy and safety of neoadjuvant imatinib followed by laparoscopic surgery.

10.6 Conclusion

The standard of care for patients with localized GIST is surgery, but a multidisciplinary approach is essential for obtaining further improvements in patient survival. Based on the results of the SSG XVIII trial and EORTC 62024 trial, 2–3 years of adjuvant imatinib after complete resection can be recommended for imatinib-sensitive high-risk GIST in order to maintain a long RFS. Another promising approach is neoadjuvant therapy, and a recent phase II trial of neoadjuvant imatinib

demonstrated a favorable survival, high R0 resection rate, and high organ preservation rate in a limited patient group. Although these findings are early ones and the Japanese guideline does not recommend routine practical use, the case-by-case introduction of neoadjuvant imatinib is feasible when a tumor is marginally resectable and harbors an imatinib-sensitive genotype.

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