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ORIGINAL ARTICLE

Real-world data on the efficacy and safety of adjuvant chemotherapy in Japanese patients with a high-risk of gastrointestinal stromal tumor recurrence

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Abstract

Background Complete surgical resection is the only treatment for resectable gastrointestinal stromal tumors (GISTs). Three-year adjuvant chemotherapy (AC) is recommended for patients with high-risk GISTs. However, there are scarce data on this topic in Japan. We aimed to study the efficacy and safety of AC in Japanese patients with high-risk GISTs.

Methods Patients with high-risk GISTs who received complete resections during 1992–2019 in our hospitals were included in this retrospective study. We evaluated patients' treatments with or without AC, completion rates, adverse events (AEs), recurrence-free survival (RFS), and overall survival (OS).

Results Overall, 89 patients categorized as high risk were enrolled in this study. Fifty-five patients received AC (AC group), and 34 patients did not receive AC (control group). Twenty-three (41.8%) patients experienced Common Terminology Criteria for Adverse Events Grade 2 or higher AEs. At a median follow-up of 61.6 months, 41 (74.5%) patients completed the planned treatment (including six patients with ongoing treatment), whereas 14 (25.4%) patients did not complete the treatment owing to the development of AEs (nine patients), patients' request (three patients), recurrence (one patient), and mutational analysis (one patient). Comparing the data between the treatment and control groups, the RFS rate was significantly better for the AC group ($P < 0.001$). However, there was no significant difference in the OS rate between the two groups.

Conclusion Postoperative AC was well tolerated by Japanese patients at an acceptable rate, and its use may reduce the risk of recurrence in patients with high-risk GISTs.

Keywords Adjuvant chemotherapy · High-risk GIST · Imatinib

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Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors specific to the gastrointestinal tract and are generally defined as KIT-positive tumors, with characteristic histological features [1]. In spite of the efficacy of molecular-targeted therapy, surgical resection is still the only treatment [2, 3]. However, since there are some patients who have recurrence after complete resection, a multidisciplinary treatment strategy, which includes a combination with imatinib, has been developed for patients with a high risk of GIST recurrence.

DeMatteo et al. reported the feasibility and efficacy of 1-year imatinib adjuvant chemotherapy (AC) after surgery. Their results showed that the AC group had longer

recurrence-free survival (RFS) than the placebo group [4]. However, because the study included a significant number of patients with low and intermediate risks of recurrences with GISTs ≥ 3 cm, the target GIST patients who were eligible for adjuvant treatment were not sufficiently narrowed down. Moreover, because of the early termination of clinical trials for their benefits, the efficacy of the drugs in terms of overall survival (OS) has not yet been confirmed. In a phase III randomized clinical trial comparing the outcomes of postoperative adjuvant imatinib therapy for 1 and 3 years in patients classified as high risk according to the Fletcher classification, postoperative GISTs with a ruptured tumor were reported [5]. The study showed that not only RFS but also OS improved in the 3-year group compared to that in the 1-year group. Additional reports also showed that the 3-year group was superior with regard to long-term observation [6]. Consequently, since 2013, 3-year imatinib adjuvant therapy has been indicated for patients with a high risk of GIST recurrence in Japan.

Kanda et al. reported that AC with imatinib at a dose of 400 mg/day for 1 year was well tolerated by Japanese patients and that its use may reduce the risk of early recurrence of GIST in patients with a high risk of recurrence [7]. This trial was the only prospective study conducted on AC in Japan; however, it was a single-arm phase II trial, and the duration of AC was only 48 weeks; it did not match the current AC treatment period of 3 years. Furthermore, the follow-up periods (median 109 weeks) were too short to evaluate the efficacy. Therefore, more clinical data on Japanese patients undergoing AC who are at a high risk of GIST recurrence are required. The purpose of this study was to evaluate the efficacy and safety of adjuvant imatinib therapy in Japanese patients with high-risk GISTs.

Patients and methods

Patients

Patients were eligible if they had undergone complete gross resections of localized, primary GISTs and were deemed to be at high risk of postoperative tumor recurrence during 1992–2019 at Osaka University Hospital and Sakai City Medical Center. "High risk" was defined according to the Modified-Fletcher classification [8, 9]. In our institution, we commenced the adjuvant imatinib therapy since 2005, and since 2008, we have used this treatment for all these patients. Patients who underwent AC with imatinib after complete resection (R0) for primary GISTs during 2005–2019 were categorized into the AC group. Patients who did not receive postoperative adjuvant therapy (during 1992–2008) were categorized into the historical control group (control group). Between 2005 and 2010, in general, we used 1-year imatinib treatment duration and, after 2011, a 3-year imatinib duration.

Patient background characteristics, neoadjuvant imatinib therapy implementation status, duration of AC, completion rate, adverse events (AEs), imatinib blood levels at 3–6 months after the initiation of AC, and survival were evaluated. For long-term prognosis, OS was defined as the period from the date of surgery to death from any cause. RFS was defined as the time period from the date of surgery to the recurrence of the primary disease. The Human Ethics Review Committee of the Osaka University Graduate School of Medicine approved this retrospective study (No. 18424).

Adjuvant imatinib dose modification

The starting imatinib dose in all patients was 400 mg/day. We graded toxic effects with the National Cancer Institute common terminology criteria for adverse events (version 5.0). Dose modifications were made when grade 3 or 4 hematological toxicity occurred or when grade 2 to 4 non-hematological toxicity was encountered. The dose was reduced by 100 mg/day when grade 2–4 non-hematological toxicity occurred or when grade 3 or 4 hematological toxicity recurred.

Measurement of imatinib blood concentration

The measurement of the trough imatinib plasma concentration has been covered by the medical insurance since 2012 in Japan. Since then, we routinely measured it in all patients treated by imatinib. In general, imatinib blood levels were routinely measured at 3–6 months after the initiation of AC. Clinical data were recorded during follow-up at outpatient clinics. Physical examinations for toxicity and laboratory tests for hematology and biochemistry were performed when blood samples for imatinib assays were collected. AEs were documented and graded according to the Common Terminology Criteria for Adverse Events (version 4.0). Peripheral blood for imatinib assay was collected from 26 patients within 24 ± 2 h of the last imatinib administration. The plasma was immediately separated at 4ºC by centrifugation and kept at − 20 ºC until measurement.

Statistical analysis

Statistical analyses were performed using statistical software (JMP PRO, version 16.0.0, SAS Institute, Cary, NC). OS and RFS were assessed using the Kaplan–Meier method, and comparisons were made using the log-rank test. To evaluate the correlation between drug blood levels and AEs, receiver-operating characteristic (ROC) curve and area under the ROC curve (AUC_{ROC}) were analyzed. P values < 0.05 were considered to indicate statistical significance.

Results

Patient characteristics

Figure 1 shows a flowchart of the patient selection process. The total number of patients with primary GISTs that were resected was 369. First, we excluded patients with R2 resection ($n=17$). Using the Modified-Fletcher Classification in the postoperative evaluation of all the patients, we also excluded low- and intermediate-risk patients ($n=263$). Finally, 89 patients were included in the analysis. Table 1 shows the details of patients' background features. Of the 65 patients with mutation data available, *KIT* exon 11 was the most common ($n=53$), followed by KIT exon9 ($n=5$), *PDGFRA* exon 18 ($n=3$), *PDGFRA* exon 12 ($n=2$) and wild type ($n=2$). One patient who was proven to have a *PDGFRA* exon 18 mutation after the initiation of AC, had stopped AC. A total of 89 patients, i.e., 55 in the AC group and 34 in the control group, were included in the analysis. The median follow-up period in the AC group was 53.4 months (19.7–147.6 months) and that in the control group was 78.3 months (0.8–222.8 months). The median duration of treatment in the imatinib group was 26.2 months (0.4–121.0 months); 1-year group ($n=12$), 11.2 months (1.7–36.5 months); and 3-year group ($n=43$), 35.6 months (0.4–121.0 months).

Table 2 shows the outcomes of adjuvant imatinib chemotherapy. Thirty-five patients (63.6%) completed treatment, and six patients (10.9%) underwent treatment. Fourteen cases (25.4%) of treatment interruption were observed. Reasons for the interruption of the chemotherapy were AEs in nine cases, patient preferences in three cases, recurrence in one case, and a platelet-derived growth factor receptor alpha (*PDGFRA*) exon 18 mutation in one case. The relative dose intensity (RDI) of all cases was $68.3 \pm 37.7\%$. The RDI of the protocol completion group was $85.2 \pm 25.7\%$, whereas the RDI of the protocol interruption group was $18.6 \pm 17.2\%$.

Long-term outcomes

Figure 2 shows the survival curve of postoperative AC, comparing OS and RFS between the AC group and the control group. The 5-year OS rates in patients assigned to the imatinib group and those assigned to the no chemotherapy group were 94.4% and 83.5%, respectively (log-rank: $P=0.51$), and the corresponding 5-year RFS rates were 69.5% and 49.0%, respectively (log-rank: $P<0.001$).

The RFS curve validated the postoperative course in three groups: those who were able to complete AC (protocol completion group), those unable to adjuvant complete chemotherapy (protocol interruption group), and the control group (Fig. 3). There was a significant difference in the RFS among the three groups ($P<0.001$). The protocol completion group had the best prognosis, and the control group had the worst prognosis. There was a significant difference between the protocol completion and protocol interruption groups ($P=0.004$). On the contrary, there was no significant difference between the protocol interruption and control groups ($P=0.49$). There was a significant difference between the protocol completion group and the control group ($P<0.001$).

As shown in Fig. 4, there was no significant difference in the OS curve ($p=0.103$). On the other hands, the RFS curve demonstrated alterations, which clarifies the influence of stopping imatinib. There was a significant difference in RFS between the control group after the surgery

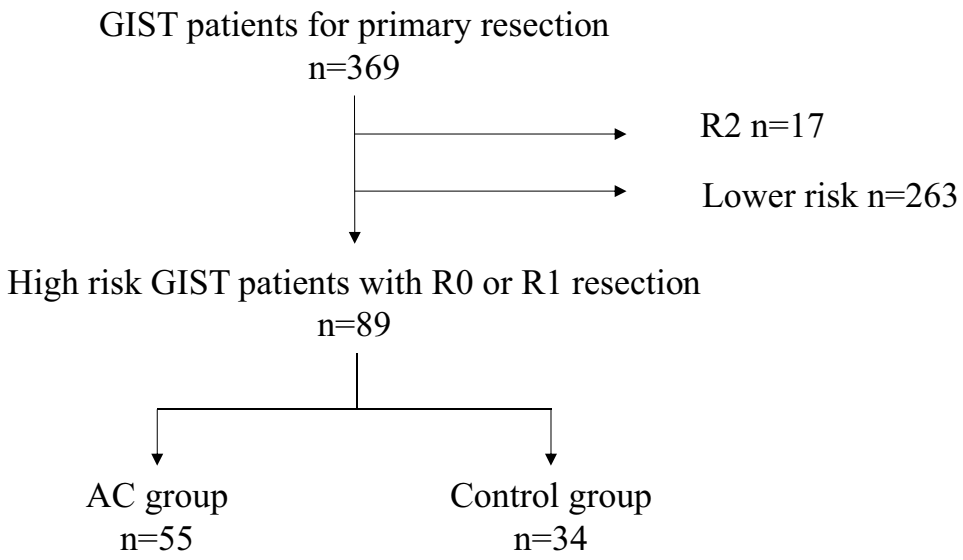

Fig. 1 Flowchart of the patient selection process. Of 281 patients who had resection of primary gastrointestinal stromal tumors (GIST), 64 were categorized as high-risk patients with R0 or R1 resection using modified-Fletcher's classification

Table 1 Patients' characteristics

	AC group $n=55$	Control group $n=34$	*P* value
Age (years)*	64 (31–83)	64 (31–76)	0.77
Sex			0.80
Male	26	17	
Female	29	17	
Tumor site			0.21
Stomach	35	15	
Small intestine	12	10	
Large intestine	4	6	
Duodenum	3	3	
Esophagus	1	0	
Tumor size (cm)*	9.0 (2.0–37.0)	6.0 (1.8–15.0)	0.002
Mitotic index (per 50 HPFs)	8 (0–400)	8 (0–200)	0.59
Not available	3	1	
Mutation status			0.24
Exon 11	36	17	
Exon 9	2	3	
PDGFRA 18	1	2	
PDGFRA 12	1	1	
Wild type	0	2	
Not examined	15	9	
Tumor rupture	11 (20.0%)	1 (2.9%)	0.012
Neoadjuvant imatinib therapy	12 (21.8%)	4 (11.8%)	0.23
Duration of imatinib therapy(month)			
1-year group ($n=12$)	11.2 (1.7–36.5)		
3-year group ($n=43$)	35.6 (0.4–121.0)		
Imatinib after recurrence			0.660
Yes	8	14	
No	1	3	

and the AC group after the completion of postoperative AC ($P=0.029$), and the 5-year RFS rates were 62.4% (AC group) and 49.0% (control group).

Adverse events

The detailed classification of AEs due to imatinib therapy is shown in Table 3. Of the 55 patients, 45 (81.8%) experienced some AEs. The most common AEs experienced were edema (32 cases, 58.2%), followed by rash (21 cases, 38.2%), diarrhea (11 cases, 20.0%), Grade 2 or higher (23 cases, 41.8%), and grade 3 or higher AEs (10 cases, 18.2%). Of the 14 cases of treatment discontinuation, nine were due to AEs (Table 2). The causes of imatinib treatment discontinuation were rash in two cases, and edema, neutropenia, neuropathy, acute kidney injury, heart failure, interstitial pneumonia, and photosensitivity in one case each.

Imatinib blood levels

Imatinib blood levels were measured in 26 patients (Table 4). At the time of imatinib blood level measurement, 9 patients (34.6%) experienced some AEs, while 17 patients (65.4%) did not. Imatinib blood levels were significantly higher in patients with AEs (patients with AEs [median: 1520 (ng/mL), range: 799–2624 (ng/mL)] vs. patients without AEs: [median: 736 (ng/mL), range: 163–1408 (ng/mL)], $P=0.002$) (Fig. 5). From the ROC analysis, 1178 ng/mL was the threshold imatinib trough concentration for AEs (sensitivity 77.8%, specificity 71.9%, AUC_{ROC}: 0.88).

Discussion

In spite of the recent oncologic success of molecular-targeted therapy, the curative treatment of choice continues to be surgery. Additionally, perioperative chemotherapy

Table 2 Outcomes of adjuvant chemotherapy

Imatinib group $n=55$	
Ongoing or finished on schedule (protocol group)	41 (74.5%)
-Ongoing	6 (10.9%)
-Finished on schedule	35 (63.6%)
Relative dose intensity (RDI) (%) **	68.3 ± 37.7
-RDI of protocol group **	85.2 ± 25.7
-RDI of treatment interruption group **	18.6 ± 17.2
Stop the treatment	14 (25.4%)
Adverse events	9
Rash	2
Edema	1
Neutropenia	1
Neuropathy	1
Acute kidney injury	1
Heart failure	1
Interstitial pneumonia	1
Photosensitivity	1
Patients request	3
Recurrence	1
PDGFRA exon18	1

* Data are presented as median (interquartile range), ** Data are presented as mean ± SD

has been developing. The ACOSOG Z9001 study showed that 1 year of AC with imatinib prolonged RFS [4], and the SSGXVIII/AIO study showed that 3 years of AC with imatinib prolonged not only RFS but also OS [5, 10]. This trial showed that the 3-year imatinib treatment prolonged OS compared to the 1-year imatinib treatment; with this evidence, the 3-year imatinib treatment has been established as a standard approach for patients with a high recurrent risk of GIST. Based on this process, the strategy for AC for these patients in our hospitals had changed from 1 year ($n=12$) to 3 years ($n=43$) for long-term treatment. In our study, because the AC group had a larger tumor size and a higher rate of tumor rupture, it was considered to have a higher possibility of recurrence than the control group. However, in spite of the higher risk, we observed an improvement in RFS with AC compared to that in the control group. In addition, there was only one case of recurrence during AC, confirming the high efficacy of the treatment. On the contrary, we could not confirm the advantage in OS. This might be due to the high clinical efficacy of imatinib after recurrence [11, 12]. Furthermore, AC for 3 years after surgery has become the standard treatment [5, 6], but based on this retrospective study, approximately 30% of patients were treated only for 1 year, affecting the long-term prognosis. In addition, the protocol interruption group was less effective in preventing recurrence than the protocol completion group, and there was no significant difference in the long term compared to that in the control group. We speculated that adequate duration might have contributed to the superiority in OS. Recently, there has been discussion on extending the AC duration to longer periods, such as 5 years and more, as extended treatment might lead to contribution to OS to a greater extent.

There have been few reports of postoperative adjuvant GIST in Japan; the results of Kanda et al. were comparable to those of the Z9001 study in terms of treatment completion rate and the incidence of adverse drug reactions, indicating that imatinib adjuvant therapy can be administered to Japanese patients with GIST and to Western patients [4, 7]. The complications of Grade 3 or higher in both studies were also similar (34.4% vs. 30.9%). On the contrary, Grade 3 or higher neutropenia incidence showed a higher tendency in

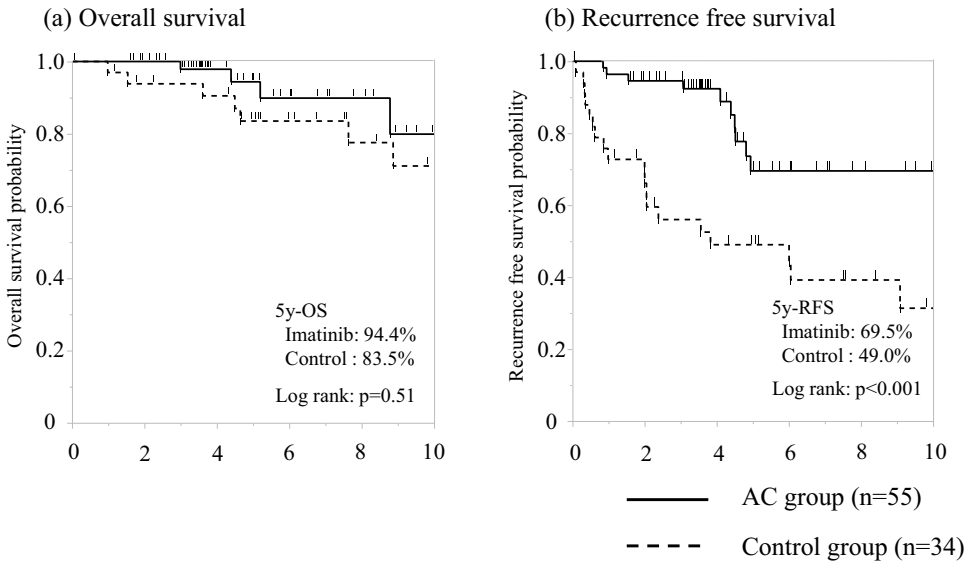

Fig. 2 Survival curves for verifying postoperative adjuvant chemotherapy. Comparison of overall survival (**a**) and recurrence-free survival (**b**) between the imatinib group and the historical control group. The 5-year overall survival rates of patients assigned to the imatinib group and those of patients assigned to the no-chemotherapy group are 94.4% vs 83.5% (log-rank; $p=0.51$), and the 5-year recurrence-free survival rates are 69.5% vs 49.0% (log-rank; $p<0.001$)

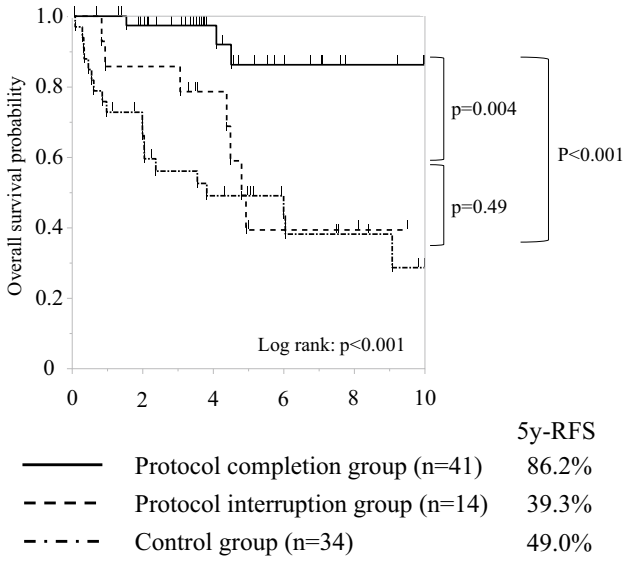

Fig. 3 Recurrence-free survival curve for validating the postoperative course. There was a significant difference in recurrence-free survival among the three groups ($p<0.001$). The protocol completion group had the best prognosis, and the historical control group had the worst prognosis. There was a significant difference between the protocol completion group and the control group ($p<0.001$) and between the protocol completion group and the protocol interruption group ($p=0.004$). However, there was no significant difference between the protocol interruption group and the control group ($p=0.49$)

the study by Kanda et al. than in the Z9001 study (14.1% vs. 3.6%). Our study showed that the total AEs of Grade 3 or higher accounted for 18.2% of the total cases, and neutropenia occurred in 7.3% of patients, which was similar to the data in Kanda's report. Furthermore, three patients in the 1-year group stopped imatinib (25.0%) and 11 patients in 3-year group stopped imatinib (25.6%). Because 8 of 11 patients in 3-year group stopped imatinib within 1 year, AC for three years may be as feasible as AC for 1 year. These results confirmed the tolerability of AC for 3 years in Japanese patients. Nishida T et al. recently reported the adherence to guidelines concerning about AC for high-risk GISTs by the Japanese registry. In this report, AC was administered to 81% of high-risk GIST patients in Japan and the tumor size, mitotic rate, and tumor rupture were found to be positive selection factors for AC, while age and PS were negative selection factors. [13]. It was equivalent to our data (89.8%) since 2011 when AC was established in Japanese guideline. Five patients did not receive AC, 3 for financial reasons, 1 for AE during NAC, and 1 for patient's request. Taken together, these findings indicate that AC has been generally widespread and acceptable for high-risk patients in the real world.

Therapeutic drug monitoring (TDM) according to the blood concentration of imatinib, which has been implemented in leukemia and other diseases, may be effective for the management of AE [14–16]. Imatinib is characterized by large interindividual pharmacokinetic variability, reflecting the large spread of concentrations observed using standard

(a) Overall survival curves for validating the postoperative course

(b) Recurrence-free survival curves for validating the postoperative course

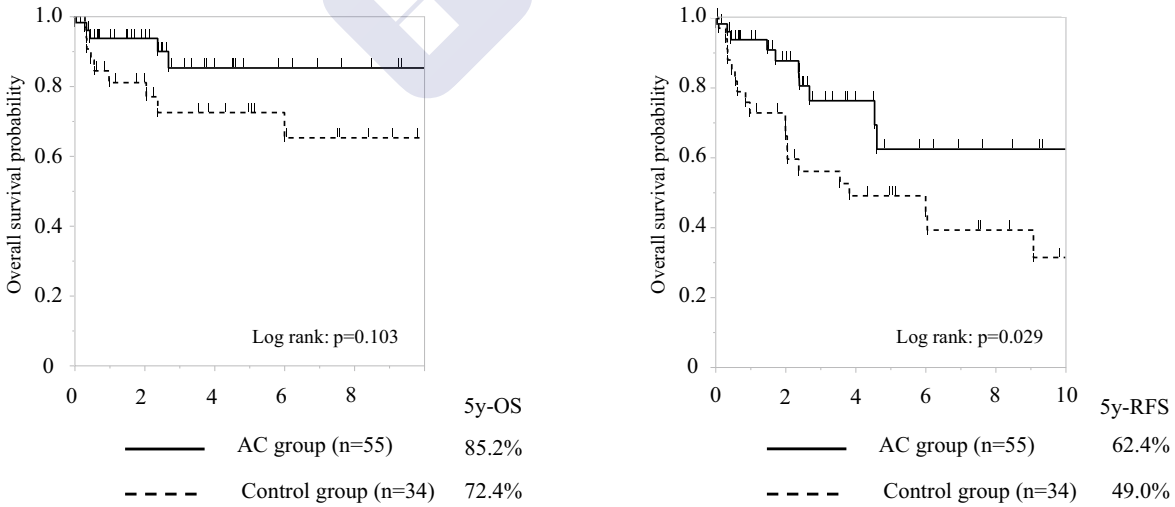

Fig. 4 Overall and recurrence-free survival curves for validating the postoperative course (comparison of the control group and the imatinib group after completion of chemotherapy). **a** Overall survival curves for validating the postoperative course, and **b** recurrence-free survival curves for validating the postoperative course. There was no significant difference in OS (log-rank; $p=0.103$). On the other hands, there was a significant difference in RFS between the control group and the AC group after completing chemotherapy (log-rank; $p=0.029$). The 5-year recurrence-free survival rates are 49.0% in the control group and 62.4% in the AC group.

Table 3 Adverse events related to postoperative chemotherapy

	All grade	≥Grade2	≥Grade3
Total	45 (81.8%)	23 (41.8%)	10 (18.2%)
Edema	32 (58.2%)	14 (25.5%)	2 (3.6%)
Rash	21 (38.2%)	16 (29.0%)	2 (3.6%)
Diarrhea	11 (20.0%)	–	–
Neutropenia	6 (10.9%)	6 (10.9%)	4 (7.3%)
Fatigue	6 (10.9%)	–	–
Mucositis oral	4 (7.3%)	–	–
Anemia	3 (5.4%)	1 (1.8%)	–
Platelet count decreased	2 (3.6%)	–	–
Neuropathy	1 (1.8%)	1 (1.8%)	1 (1.8%)
Acute kidney injury	1 (1.8%)	1 (1.8%)	1 (1.8%)
Heart failure	1 (1.8%)	1 (1.8%)	1 (1.8%)
Interstitial pneumonia	1 (1.8%)	1 (1.8%)	1 (1.8%)
Photosensitivity	1 (1.8%)	1 (1.8%)	-
Alopecia	1 (1.8%)	1 (1.8%)	–
Other	8 (14.5%)	–	–

dosages, ranging from 150 to 3910 ng/mL at the end of the dosage interval (trough concentration) [17]. Moreover, in cases of AEs with imatinib, blood concentration monitoring combined with molecular monitoring of the treatment responses may be a useful indicator of treatment, especially in patients with a small body size [18]. In this study, TDM was also used in 26 patients [median: 982 (ng/mL), range: 163–2624 (ng/mL)] (Table 4). The median blood levels of imatinib in patients with and without AEs were 1520 and 736 (ng/mL), respectively, which were significantly higher in patients with AEs. Yanzhe Xia et al. [19] previously reported that the blood levels of imatinib were correlated with periorbital and limb edema, anemia, and rash in a large number of Chinese patients. In our study, edema and rash were also related to the blood levels of imatinib. In addition, grade 3 AEs, such as chronic kidney disease and neutropenia, were also observed in patients with high blood levels, which were reported to have a tendency appearing in patients with higher imatinib blood levels [19, 20]. Because the relationship between AEs and blood levels of imatinib has not yet been validated in Japanese GIST patients, it would be

Table 4 Relationship between imatinib blood levels and the development of adverse events

Case (N0.)	Age (Year)	Sex	Drug dose (mg)	Adverse events	blood level of imatinib (ng/mL)
1	64	Male	200	Acute kidney injury Grade3	2624
2	64	Female	300	Rash: Grade3	2080
3	56	Male	300	Rash: Grade2	1809
4	61	Male	400	Edema: Grade2	1778
5	62	Female	400	Neutropenia: Grade 2	1520
6	74	Female	200	None	1408
7	70	Female	400	Edema: Grade2	1348
8	66	Female	400	Hair loss: Grade2	1178
9	50	Male	400	None	1073
10	69	Female	300	None	1053
11	83	Female	200	None	1041
12	45	Male	400	None	1039
13	51	Female	300	None	1033
14	47	Female	300	None	931
15	74	Male	400	None	853
16	69	Female	300	Edema: Grade3	810
17	79	Male	300	Rash: Grade2	799
18	44	Female	400	None	736
19	56	Male	400	None	661
20	31	Female	200	None	656
21	70	Female	300	None	656
22	42	Female	100	None	575
24	71	Male	300	None	570
25	68	Female	200	None	530
25	66	Female	100	None	370
26	32	Female	400	None	163

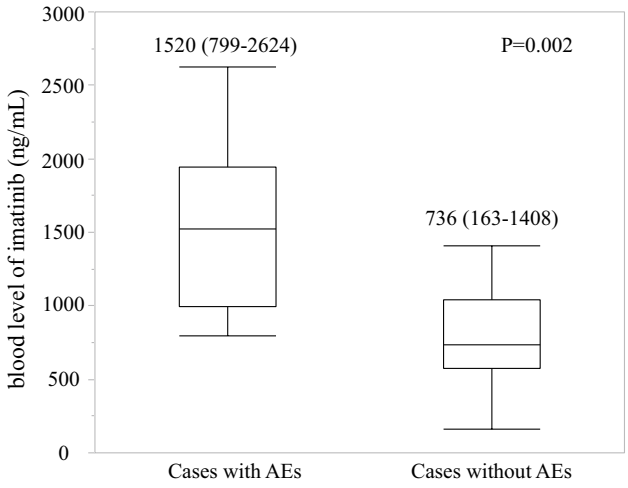

Fig. 5 Relationship between imatinib blood levels and the development of adverse events (Grade ≥ 2). Imatinib blood levels were measured in 26 patients. Imatinib blood levels were significantly higher in patients with AEs ($p = 0.002$)

necessary to establish a system to measure the imatinib blood levels to optimize the dose of imatinib.

Understanding the timing of the recurrence after the discontinuation of AC is essential for the development of GIST follow-up strategies [21]. We have previously reported that the postoperative surveillance of GISTs should be at least 5 years [22]. In this study, the RFS curves of the imatinib group after the completion of AC showed significantly better outcomes than those of the surgery-only group. This suggests that imatinib AC might delay the recurrence of GIST and that a more extended follow-up period may be necessary after AC. Therefore, a more extended follow-up period may be necessary for the AC group.

Activating mutations in *KIT* or *PDGFRA* are thought to be the major molecular drivers of most GISTs. It is related to the drug sensitivity. In general, *KIT* exon 11 mutations are most sensitive to imatinib, whereas *PDGFRA* exon 18 mutations leading to Asp842Val (D842V) are considered imatinib-resistant both in vitro and in vivo [23, 24]. Therefore, there is a consensus in the European Society for Medical Oncology guideline that *PDGFRA* D842V-mutated GISTs should not be treated with any adjuvant therapy. In this study, one patient who was proven to have a *PDGFRA* exon 18 mutation later, had stopped AC in the midst of treatment. Recently, avapritinib, a drug targeting Asp842Val, has been approved by the US Food and Drug Administration. Avapritinib has shown high efficacy in unresectable GISTs in Asp842Val patients [25], with the possibility of being effective as adjuvant therapy. It might become a hopeful treatment as AC. In any case, we recommend that mutation analysis be mandatory to AC.

This study has several limitations. First, this was a retrospective cohort study conducted at few hospitals. Therefore, we could compare the AC group only with the control group, which led to some bias. Furthermore, the AC group was not a homogeneous treatment group; this study included a period of transition in the treatment strategy by our hospitals. Second, we tried to analyze the sensitivity of AC by the genotyping, however, the patients having mutation rather than *KIT* exon 11 were so small that we couldn't draw a definite conclusion from our data. Third, the study included three patients who continued receiving the drug by the patient's request after 3 years' AC. However, whether extending exposure to imatinib beyond 3 years will further delay recurrence by shifting the RFS curve or by preventing the disease recurrence remains unclear. It is also necessary to extract higher risk among the high-risk patients to avoid unnecessary long treatment. This might be necessary to conduct large-scale prospective studies to confirm the period and candidate for longer AC.

In conclusion, this study confirmed the acceptability of imatinib for high-risk GIST in the Japanese population. Postoperative AC was well tolerated with acceptable treatment courses, and its use may reduce the risk of recurrence in patients with high-risk GISTs.

Declarations

Conflict of interest The authors have no conflicts of interest to declare.

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