Benefit of imatinib adjuvant therapy for patients with intermediate risk gastrointestinal stromal tumor: a multi-center retrospective analysis in China

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Abstract

Background The benefit of postoperative imatinib therapy on intermediated risk gastrointestinal stromal tumor patients were still under debate. Thus, the present study aims to investigate the impact of imatinib adjuvant therapy on the prognosis of intermediate risk gastrointestinal stromal tumor patients.Methods From January 2000 to April 2018, a total of 450 intermediate risk gastrointestinal stromal tumor patients received R0 resection from eight centers in China were enrolled. The clinicopathological features and prognosis of patients were analyzed. Discrete variables were analyzed using the Chi-square test or Fisher's exact test. Significant predictors for survival identified by univariate analysis and multivariate analysis. Disease-free survival was evaluated by Kaplan-Meier method.Results Among the 450 patients, 109 patients (24.2%) received imatinib treatment. The recurrence rate of patients with and without imatinib treatment was 7.3% and 5.3%, respectively. For the entire cohort, gene mutational status was the only independent risk factor for disease-free survival of patients though univariate and multivariate analysis (P=0.028). For patients without imatinib treatment, tumor location (P=0.025) and gene mutation status (P=0.040) were prognostic factors in univariate analysis. However, only gene mutational status was independent prognostic factor (P=0.037). The disease-free survival of gastrointestinal stromal tumor with exon 11 deletion mutation with and without imatinib treatment were comparable (P=0.531).Conclusions Imatinib adjuvant treatment could not improve the prognosis of intermediate risk gastrointestinal stromal tumors. Intermediate gastrointestinal stromal tumors with exon 11 deletion mutation or non-gastric location may be candidates for imatinib treatment.

Background

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract with the incidence between 10 and 15 cases per million[1]. Interstitial cells of Cajal, pacemaker cells of the gastrointestinal tract, are considered as the precursor cells of GISTs[2]. GISTs are seen most commonly in the stomach, followed by small intestine, and colorectum, etc.[3]. Complete surgical resection remains the only curative treatment for localized GISTs[4]. However, over 40% of patients will develop recurrence or metastasis after surgery[5].

With demonstrated dramatical effect of imatinib in advanced GISTs, it has been recommended as adjuvant therapy for GIST patients after R0 resection[6]. Clinical trial of Z9001 demonstrated that adjuvant imatinib therapy could improve recurrence-free survival (RFS) compared with placebo after the resection of primary GIST[7]. Further, SSGXVIII/AIO trial found that 3 years of imatinib could significantly improve RFS and overall survival of high risk GIST compared with 1 year of adjuvant imatinib therapy[8]. However, the benefit of imatinib adjuvant therapy for intermediate risk GISTs was still unclear and under debate. Up to date, only two retrospective studies analyzed the impact of imatinib adjuvant therapy for intermediate risk GISTs. Wu et al. reported that adjuvant imatinib therapy could improve RFS of intermediate risk GISTs[9]. However, Fu et al. did not find any significant benefit for intermediate risk GISTs with imatinib adjuvant treatment[10]. Thus, the present study aims to investigate the impact of imatinib adjuvant therapy for intermediate risk GIST patients.

Methods

From January 2000 to April 2018, a total of 450 patients with intermediate risk GISTs were enrolled in our present study. Data of patients were from the following eight centers in China: Zhongshan Hospital, Fudan University (n = 181), Xijing Hospital, the Fourth Military Medical University (n = 121), Cancer Hospital of China Medical University (n = 64), the First Affiliated Hospital of Chongqing Medical University (n = 40), Tangdu Hospital, the Fourth Military Medical University (n = 14), the First Hospital of Lanzhou University (n = 13), Cancer Hospital, the Xinjiang Medical University (n = 12) and the Affiliated Hospital of Qinghai University (n = 5). This study was approved by the Ethics Committee of each center, and written informed consent was obtained from all patients before surgery.

The inclusion criteria were: 1. diagnosed as GISTs, 2. without other malignant tumor, 3. without distant metastasis at diagnosis, 4. without preoperative imatinib therapy, 5. with R0 resection, 6. confirmed as intermediate risk GISTs through pathological examination based on the modified NIH consensus classification system[11],7. treated with postoperative imatinib therapy at a dose of 400 mg/day for at least 12 months, 8. with follow up data.

Clinicopathological data including gender, age, tumor location, tumor size, mitotic index, Ki-67, histological type, CD117, CD34 and DOG-1 expression and mutational status were collected. Data about prognosis including recurrence and disease related death were also recorded.

Data were processed using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA). Discrete variables were analyzed using the Chi-square test or Fisher's exact test. Significant predictors for survival identified by univariate analysis were further assessed by multivariate analysis using logistic regression analysis. Evaluation for disease-free survival (DFS) were obtained by Kaplan-Meier method. The P values were considered to be statistically significant at 5% level.

Results

The clinicopathological features of the entire cohort were summarized in Table 1. There were 215 male (47.8%) and 235 female (52.2%). The median age were 58 years (50 to 65 years). Most tumors were located in the stomach (440/450, 97.8%), the rest 10 tumors were located in esophagus (3), duodenal (3), small intestine (2) and rectum (2). Three hundred and seventy tumors displayed spindle cell morphology (370/418, 88.5%), 28 tumors displayed epithelioid morphology (28/418, 6.7%), and 20 tumors displayed mixed morphology (20/418, 4.8%). The positive rate of CD117, CD34 and DOG-1 were 95.4%, 97.2% and 93.5%. One hundred and sixty-six patients (36.9%) received c-kit/PDGFR gene mutation status examination. One hundred and nine patients (24.2%) received imatinib therapy. The median follow up time was 48 months (27 to 74 months). In total, 8 patients suffered from recurrence or metastasis in the treatment group (7.3%), and 18 patients suffered from recurrence or metastasis in the control group (5.3%). The most common location of metastasis was liver (15/26, 57.7%).

Table 1
Clinicopathological features of patients.

Characteristics	Treatment group (n = 109)	Control group (n = 341)	P value
Gender			
Male	41	174	0.016
Female	68	167	
Age (years)			
≤60	68	185	0.150
>60	41	156	
Tumor location			
Stomach	108	332	0.463
Other	1	9	
Tumor size (cm)			
≤ 5	36	145	0.092
6–10	73	196	
Mitotic index (50HPF)			
≤ 5	73	196	0.092
6–10	36	145	
Mutational status			
Exon 11 deletion mutation	24	31	0.277
Exon 11 nondeletion mutation	23	40	
Exon 9/12/18 mutation	3	10	
Wild type	9	26	

The risk factors for the prognosis of entire cohort were analyzed using univariate and multivariate analysis and summarized in Table 2. The results showed that only gene mutational status was independent prognostic factor. Imatinib treatment was not associated with the prognosis of patients. The DFS of patients with and without imatinib treatment was comparable (Fig. 1). The DFS of patients with exon 11 deletion mutation was significantly lower than that of exon 11 nondeletion mutation and other gene mutational status (Fig. 2). Interestingly, the DFS of patients with non-gastric tumors was significantly lower than that with gastric tumors (Fig. 2). However, in the univariate analysis, the prognostic value of tumor location was on the boundary of significance (P = 0.060).

Table 2

Risk factors for DFS according to univariate and multivariate analysis.

	Univariate analysis			Multivariate analysis		
Characteristics	β	Hazard ratio (95% CI)	P value	β	Hazard ratio (95% CI)	P value
Gender(male/female)	-0.240	0.787(0.364–1.701)	0.542	-	-	-
Age(≤ 60/>60)	0.164	1.178(0.546–2.542)	0.677	-	-	-
Tumor location(stomach/other)	-1.388	4.006(0.944–17.007)	0.060	-	-	-
Tumor size(≤ 5/6–10)	-0.201	0.818(0.378–1.770)	0.610	-	-	-
Mitotic index(≤ 5/6–10)	0.362	1.436(0.665-3.100)	0.357	-	-	-
Imatinib treatment(yes/no)	0.438	1.549(0.668–3.596)	0.308	-	-	-
Mutational status(Exon 11 deletion mutation/ Other mutation and WT	-1.482	0.227(0.058–0.888)	0.033	-1.545	0.213(0.054–0.847)	0.028
Abbreviations: CI, confidence interval.						

The risk factors for the prognosis of patients without imatinib treatment were analyzed using univariate and multivariate analysis and summarized in Table 3. The results showed that tumor location and gene mutational status were risk factors for the prognosis of patients. However, only gene mutational status was independent prognostic factor. Patients with exon 11 deletion mutation or non-gastric tumors were associated with poor DFS (Fig. 3).

Table 3

Risk factors for DFS of control group according to univariate and multivariate analysis.

	Univariate analysis			Multivariate analysis		
Characteristics	β	Hazard ratio (95% CI)	P value	β	Hazard ratio (95% CI)	P value
Gender(male/female)	-0.452	0.637(0.247–1.642)	0.350	-	-	-
Age(≤ 60/>60)	0.123	1.131(0.0.448–2.850)	0.795	-	-	-
Tumor location(stomach/other)	1.687	5.405(1.233–23.689)	0.025	-12.545	-	0.991
Tumor size(≤ 5/6–10)	-0.277	0.758(0.300-1.912)	0.557	-	-	-
Mitotic index(≤ 5/6–10)	0.508	1.662(0.655–4.217)	0.285	-	-	-
Mutational status(Exon 11 deletion mutation)/Other mutation and WT	-1.738	0.176(0.033–0.928)	0.040	-1.767	0.171(0.032–0.909	0.037
Abbreviations: CI, confidence interval.						

Further, the value of imatinib treatment for patients with exon 11 deletion mutation were analyzed. Survival analysis showed that DFS of the two groups were comparable (Fig. 4). However, compared with patients without imatinib treatment, the recurrence rate of patients with imatinib treatment was lower (2/24, 8.3% vs 5/31, 16.1%).

Discussion

Microscopic complete resection without rupture is the optimal standard treatment for localized GISTs. Although received R0 resection, over 40% of patients will develop recurrence or metastasis after surgery[5]. With demonstrated effect of imatinib in advanced GISTs, it has been recommended as adjuvant treatment of GIST patients[6]. Although Z9001 trial demonstrated that 1 year of adjuvant imatinib therapy could improve RFS of GIST patients[7], and SSGXVIII/AIO trial found that 3 years of imatinib therapy could improve RFS and overall survival of high risk GIST compared with 1 year treatment[8], the benefit of imatinib adjuvant therapy for intermediate risk GIST was still unclear. In our present study, we found that imatinib adjuvant therapy could not improve the DFS of intermediate risk GIST patients. For both the entire cohort and control group, exon 11 deletion mutation was independently associated with poor prognosis. Although the prognosis of non-gastric GIST was worse than gastric GIST, this has not been demonstrated during multivariate analysis.

Up to date, only two studies investigated the impact of imatinib adjuvant therapy on the prognosis of intermediate risk GISTs. Fu et al. analyzed 85 cases of intermediate risk GIST in single center and found no benefit for intermediate-risk GIST to accept imatinib adjuvant treatment[10]. Wu et al. analyzed 192 cases of intermediate risk GIST based on two centers and reported that adjuvant imatinib could improve the prognosis of intermediate risk GIST, particularly in tumors in small intestine and rectum or with exon 11 deletion mutation[9]. However, our present study, which enrolled 450 cases of intermediate risk GIST from 8 centers, did not find any benefit of imatinib adjuvant therapy for intermediate risk GIST.

Besides tumor size and mitotic index, location is also associated with the prognosis of GISTs, and non-gastric GISTs were reported to be more aggressive than gastric GISTs in clinical course[12, 13]. In the study reported by Fu et al.[10], the prognosis of non-gastric GISTs was significantly worse than gastric GISTs. However, this has not been confirmed by multivariate analysis. Wu et al. demonstrated that non-stomach location was independently associated with poor prognosis of GISTs through multivariate analysis[9]. In our present study, although the prognosis of non-gastric GISTs was worse than gastric ones, the correlation disappeared in the multivariate analysis. This could be partially explained by the different constituent ratio of gastric and non-gastric GISTs among the three studies. In the published two studies, the proportion of non-gastric GISTs were 37.5%[9] and 27.1%[10], respectively. However, the proportion of non-gastric GISTs were only 2.2% (10/450) in our present study. Although DFS of gastric GISTs was significantly better than non-gastric ones, the 95% confidence interval could not be calculated out in the multivariate analysis due to the extremely small sample size and extremely low constituent ratio of non-gastric GISTs.

It was reported that the recurrence rate of was 3.6% for gastric GISTs with tumor size from 5.1 to 10 cm and mitotic index less than or equal to 5/50 HPF, 16.0% for gastric GISTs with tumor size from 2.1 to 5 cm and mitotic index exceed 5/50 HPF, and 50–54% for non-gastric GISTs with tumor size less than or equal to 2 cm and mitotic index exceed 5/50 HPF[14, 15]. However, the above mentioned population included a proportion of high risk GISTs (mitotic index exceed 10/50 HPF) according to the modified NIH consensus classification system[11]. Thus, the recurrence rate of intermediate risk GIST in the natural clinical course was still unclear. In the study reported by Wu et al.[9], the recurrence rate was 3.6% for gastric GISTs and 18.4% for non-gastric GISTs. In our present study, the recurrence rate for gastric and non-gastric GISTs was 4.8% and 22.2%, which was consistent with previous study. As the prognosis of non-gastric GISTs was significantly worse than gastric GISTs, Wu et al.[9] further evaluated the impact of imatinib adjuvant therapy on non-gastric GISTs, and found that imatinib treatment could significantly improve RFS of non-gastric intermediate risk GISTs. In our present study, the association between tumor location and prognosis was not identified by multivariate analysis and the benefit of imatinib treatment for non-gastric GISTs could not be evaluated due to the extremely low sample size of non-gastric GISTs. However, these findings indicated that non-gastric intermediate risk GISTs may be candidates for imatinib treatment.

The genetic subtypes of GISTs were also associated with different prognostic relevance[16, 17]. It was reported that GISTs with KIT exon 11 deletions are associated with poor prognosis[18], especially in GIST

with deletions affecting codons 557–558[19–21]. However, in the Z9001 trial, the association between KIT exon 11 deletion and poor prognosis was not confirmed through multivariable analysis[22]. In the study reported by Wu et al.[9], exon 11 deletion mutation was also not associated with the prognosis of imatinib naïve GIST. However, in our present study, KIT exon 11 deletion mutation was independently associated with poor prognosis of GIST patients. Further, we wonder whether imatinib treatment could improve the prognosis of GISTs with exon 11 deletion mutation or not. Thus, the DFS of GIST with exon 11 deletion mutation with or without imatinib treatment were compared. The results showed that imatinib therapy could not improve the prognosis of GIST with exon 11 deletion mutation. This should be interpreted cautiously due to the relatively small sample size. However, imatinib therapy could significantly improve the survival of GISTs with exon 11 deletion mutation in the study reported by Wu et al.[9]. These findings indicated that intermediate risk GISTs with KIT exon 11 deletion mutation may be candidates for imatinib adjuvant therapy.

Although imatinib adjuvant therapy could not improve the prognosis of intermediate risk GISTs in our current study, 5.3% of patients without imatinib treatment did experience recurrence. Thus, identification of risk factors for recurrence would be critical important for the precision imatinib treatment of intermediate risk GISTs. It could not only lessen the economic burden of family but also avoid unnecessary adverse events of imatinib treatment. However, a series of limitations in our present study influenced the identification of candidates for imatinib treatment, such as the relatively small sample size, relatively low rate of genetic testing and imatinib treatment, and the limited parameters for analysis, etc. Thus, investigates based on large sample size should be carried out in the future in order to solve this issue.

Conclusions

Imatinib adjuvant therapy could not improve the DFS of intermediate risk GIST patients. KIT exon 11 deletion mutation and non-gastric location was associated with poor prognosis of GIST. Intermediate risk GISTs with exon 11 deletion mutation or non-gastric location may be candidates for imatinib adjuvant treatment.

Declarations

Ethics approval and consent to participate

Ethical approval for this study was granted by the Ethics Committee of each center, and all patients signed an informed consent document before surgery.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

FF, FY and ZJ conceived the study and drafted the manuscript. FF, FY, ZJ, ZGL, QQ, CN, WHJ, LB, LC, WC, ZCW, SKT, ZZC and ZHW performed the surgery and collected the data. FF performed statistical analysis. SKT, ZZC and ZHW designed and supervised the study. All authors read and approved the final version of the manuscript.

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Not applicable

Abbreviations

GISTs
gastrointestinal stromal tumors; RFS:recurrence-free survival; DFS:disease-free survival; CI:Confidence interval; HR:Hazards ratio.

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