The efficacy of adjuvant imatinib therapy in improving the prognosis of patients with colorectal gastrointestinal stromal tumours

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ABSTRACT

INTRODUCTION Although it has now been accepted that imatinib is a valid treatment for gastrointestinal stromal tumour (GIST) patients in the adjuvant setting, information on its clinical efficacy in improving the prognosis for patients with colorectal GISTs is limited.

METHODS The clinical and follow-up records of 42 colorectal GIST patients who underwent surgical resection at our institution between January 2004 and December 2013 were reviewed retrospectively. The effect of postoperative imatinib treatment on recurrence free survival and overall survival time was analysed with the Kaplan–Meier method and the multivariate Cox proportional hazards model.

RESULTS Sixteen patients were assigned to imatinib treatment (imatinib group) after surgical tumour resection while twenty-six patients did not receive any adjuvant treatment (control group). The one, three and five-year recurrence free survival rates were 100%, 90% and 77% respectively. This was significantly higher than in the control group (92%, 53% and 36%) (logrank test, $p=0.012$). The one, three and five-year overall survival rates were 100%, 91% and 68% in the imatinib group compared with 96%, 77% and 39% in the control group (logrank test, $p=0.021$). Analysis with the multivariate Cox regression model yielded similar results on the efficacy of adjuvant imatinib in prolonging both recurrence free survival (hazard ratio [HR]: 0.23, 95% confidence interval [CI]: 0.07–0.80) and overall survival (HR: 0.20, 95% CI: 0.05–0.91).

CONCLUSIONS Adjuvant imatinib therapy seems to be effective in decreasing the risk of tumour occurrence and prolonging the overall survival time in colorectal GIST patients.

KEYWORDS

Colorectal gastrointestinal stromal tumour – Adjuvant treatment – Imatinib

Accepted 17 January 2015

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Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal neoplasm that arises predominantly in the gastrointestinal tract.¹ A GIST involving the rectum and colon is an extremely rare condition, accounting for only 5–10% of all diagnosed cases² and 0.1% of all malignant colorectal tumours.³ Colorectal GISTs can be small, and may have different clinical, histological, immunohistochemical and genetic characteristics to tumours arising in other anatomic locations; they may also have a different prognosis.^{3,4} Moreover, prior studies have indicated that GISTs are associated with a significant likelihood of local and distant recurrence.^{5–7}

Surgery remains the standard and most effective treatment modality for patients with non-metastatic disease.⁸ Complete resection (R0) with negative pathological margins can be achieved in about 85% of primary GISTs.⁹ However, up to 50% of patients will develop local or distant recurrences and ultimately die of this disease.^{7,9} This suggests that surgery alone is insufficient for the management of GISTs. Unfortunately,

conventional chemotherapy and radiotherapy are generally ineffective in fighting against this adverse outcome.

Imatinib, a tyrosine kinase inhibitor that is approved for the treatment of unresectable or metastatic malignant GISTs that are positive for the CD117 protein,¹⁰ has been shown to have significant potential to improve recurrence free survival (RFS) times in the adjuvant setting in several studies.^{11,12} Nevertheless, most published series of GISTs have included very few primary colorectal patients¹³ or have not combined them with tumours from other sites when examining the efficacy of adjuvant imatinib therapy,¹⁴ mainly owing to their rarity. This makes it difficult to establish evidence-based adjuvant treatment for them. The purpose of the present study was therefore to investigate the efficacy of postoperative imatinib therapy for patients with a colorectal GIST who underwent complete surgical resection at the First Affiliated Hospital of Anhui Medical University.

Methods

This was a retrospective cohort study conducted on cases treated between January 2004 and December 2013. Patients with a colorectal GIST who underwent surgical resection were included while patients with more than one GIST or recurrent GISTs and those who received preoperative imatinib therapy were excluded. Patients with an unclear tumour size, mitotic count and date of diagnosis were further excluded from this cohort. Medical records were reviewed for data on patient age, sex, tumour site, maximal tumour diameter and clinical outcomes up to the last follow-up appointment. Follow-up information was obtained from the contributing pathologists, attending physicians, hospital records and sometimes from the patients themselves. The study protocol was approved by an institutional review committee of the ethics board of the First Affiliated Hospital of Anhui Medical University.

The histological diagnosis of the tumours was confirmed by two experienced pathologists from our institute by reviewing all pathological slices. Immunohistochemical staining for the CD117 and PDGFRA proteins was performed on tumour tissues embedded in paraffin with antibodies (Dako, Glostrup, Denmark). Specimens that stained positively for CD117 or PDGFRA were diagnosed as a GIST, irrespective of the staining results of other proteins. The risk stratification scheme for recurrence suggested by the National Institutes of Health was employed to assess the risk degree of all patients.¹⁵ Owing to the small number of patients, the first two groups ('very low risk' and 'low risk') were combined into one group, referred to in this paper simply as the low risk group.

The surgical procedure was determined independently by the physician, mainly based on tumour size and site. Adjuvant imatinib therapy was used after comprehensive assessment of patients by multidisciplinary tumour boards in our institute. Patients with a large tumour (≥ 5 cm), high mitotic count (≥ 5 mitoses per 50 high powered fields) or intraoperative tumour rupture/perforation were generally eligible for the adjuvant therapy if they showed positive immunostaining for the CD117 protein. However, patients under the age of 18 years, those with impaired renal/haematological/hepatic function or with no indication for imatinib were excluded from treatment. Subsequently, taking into account the evaluation of our institution's expert tumour committee, the attending physician also took some other factors (eg patients' willingness and affordability) into consideration when finally deciding on whether to use imatinib. Imatinib was administrated at a dose of 400mg once a day, regardless of age, sex and risk group.

Statistical analysis

Statistical analysis was performed using SAS[®] version 8.2 (SAS Institute, Cary, NC, US). Survival and recurrence were the primary endpoints. RFS was defined as the time from the date of surgery to the date of development of recurrence while overall survival (OS) was defined as the time from surgery to death from a GIST related cause. Differences between the groups were analysed by the chi-squared

(for categorical variables) or Student's t-test (continuous variables). RFS and OS were obtained using the Kaplan–Meier method and a non-parametric logrank test was performed to compare RFS and OS between the groups. Hazard ratios (HRs) and 95% confidence intervals (95% CIs) based on the Cox proportional hazards model were calculated to assess the impact of risk factors of interest on recurrence and survival.

Results

A total of 42 patients (25 men and 17 women) were included in the final analysis. The median age at diagnosis was 58 years (range: 32–79 years). The tumour size varied from 2.7cm to 12.0cm with a median size of 6.1cm. Half (50.0%) of the patients had lesions that measured 5.1–10.0cm while a third (33.3%) had lesions that were ≤ 5 cm and 16.7% had lesions of >10 cm. Immunohistochemically, CD117 was positive in 95.2% of patients whereas 4.8% of cases were PDGFRA positive.

Sixteen of the patients were assigned to adjuvant imatinib treatment after surgery at a daily dose of 400mg (imatinib group) with a median duration of 14 months (range: 6–18 months) while twenty-six patients did not receive adjuvant

Table 1 Distribution of the clinical and pathological features

	Imatinib group (n=16)	Control group (n=26)	p-value
<i>Age group</i>			0.37
≤50 years	4 (25.0%)	10 (38.5%)	
>50 years	12 (75.0%)	16 (61.5%)	
<i>Sex</i>			0.11
Male	12 (75.0%)	13 (50.0%)	
Female	4 (25.0%)	13 (50.0%)	
<i>Anatomic location</i>			0.97
Colon	11 (68.8%)	18 (69.2%)	
Rectum	5 (31.2%)	8 (30.8%)	
<i>Tumour size</i>			0.07
≤5cm	1 (6.3%)	7 (26.9%)	
5.1–10cm	7 (43.8%)	14 (53.8%)	
>10cm	8 (50.0%)	5 (19.2%)	
<i>Mitotic count</i>			<0.01
<5 per 50 HPFs	4 (25.0%)	21 (80.8%)	
≥5 per 50 HPFs	12 (75.0%)	5 (19.2%)	
<i>NIH risk categories</i>			<0.01
Low	2 (12.5%)	10 (38.5%)	
Intermediate	4 (25.0%)	12 (46.2%)	
High	10 (62.5%)	4 (15.4%)	

HPFs = high powered fields; NIH = National Institutes of Health

therapy (control group). CD117 was positive in all patients in the imatinib group while PDGFRA was positive in two patients in the control group.

The distribution of age group, sex and tumour site was similar between the two groups (Table 1). However, patients in the imatinib group were more likely to be in a higher risk group and have a higher mitotic count than their counterparts (Table 1). Although patients on imatinib seemed to have larger tumours than those in the control group, the difference was not statistically significant.

Complete follow-up data were available for all patients, with a median follow-up duration of 33.8 months (range: 9–120 months). In the imatinib group, tumour recurrence after surgery was noted in 3 patients (18.8%) and disease related death occurred in 2 patients (12.5%) while in the control group, 15 patients (57.7%) developed recurrence and 11 (42.3%) died of their GIST. The one, three and five-year RFS in the imatinib group was 100%, 90% and 77% respectively as opposed to 92%, 53% and 36% in the control group (Fig 1). Univariate analysis showed a significant difference between the groups (logrank test, $p=0.012$).

Analysis of OS yielded similar results. The one, three and five-year OS rates were 100%, 91% and 68% in the imatinib group. This was significantly higher than the corresponding figures for the control group (96%, 77% and 39%; logrank test, $p=0.021$) (Fig 2, Table 2). The multivariate Cox regression model confirmed the efficacy of imatinib in improving RFS (HR: 0.23, 95% CI: 0.07–0.80) and OS times (HR: 0.20, 95% CI: 0.05–0.91).

Discussion

Although it is now accepted that imatinib is a valid treatment for GIST patients in the adjuvant setting, information on its clinical efficacy is very limited as imatinib has only been used clinically for GISTs recently. In the case of colorectal GISTs, uncertainty is increased owing to their rarity compared with GISTs in other locations such as the stomach and small bowel. Findings from the present study may provide valuable insights for the management of colorectal GISTs.

In the current study, the one, two and three-year RFS rates in patients treated with adjuvant imatinib was 100%, 90% and 77%. This was significantly higher than the 92%, 53% and 36% in the control group. This is consistent with the results of a previous study with a comparable design where the 1, 2 and 3-year RFS in 35 patients having adjuvant therapy showed a marked improvement compared with those in the control group (100%, 88% and 88% vs 71%, 38% and 28%).¹⁶

Similar results were presented by the American College of Surgeons Oncology Group (ACOSOG) Z9001 study, in which an estimated 98% of patients in the imatinib group achieved RFS at one year, compared with 83% of patients in the placebo group.¹² These findings consistently demonstrated the significant role of imatinib in decreasing the likelihood of disease recurrence in the adjuvant setting. In the ACOSOG Z9000 study, the 5-year OS rate in patients treated with adjuvant imatinib was 83% after a median

Figure 1 Recurrence free survival

Figure 2 Overall survival

Table 2 Recurrence free and overall survival rates

	Imatinib group (n=16)	Control group (n=26)	p-value
<i>Recurrence free survival</i>			0.012
1 year	100%	92% (95% CI: 73–98%)	
3 years	90% (95% CI: 47–99%)	53% (95% CI: 31–71%)	
5 years	77% (95% CI: 34–94%)	36% (95% CI: 14–59%)	
Median	–	58 mths (95% CI: 28–88 mths)	
<i>Overall survival</i>			0.021
1 year	100%	96% (95% CI: 75–99%)	
3 years	91% (95% CI: 51–99%)	77% (95% CI: 48–91%)	
5 years	68% (95% CI: 38–88%)	39% (95% CI: 13–65%)	
Median	–	59 mths (95% CI: 57–60 mths)	

CI = confidence interval

follow-up of 7.7 years, significantly higher than the 35% in the historical control group.¹⁷

In agreement with this finding, patients treated with imatinib in the current series showed an improved OS after

a median follow-up duration of 33.8 months. Similar results were reported in study published in 2014, where 29 colorectal GIST patients treated with adjuvant imatinib for a median duration of 8 months had a markedly longer

median OS than those who did not receive adjuvant treatment (56 vs 39 months).¹⁸ These results suggest that apart from its efficacy in decreasing disease recurrence, adjuvant imatinib therapy might also have the potential to prolong the OS time.

In the present study, 3 of the 16 patients treated with imatinib (18.8%) developed recurrence during the study period, demonstrating a marked reduction of tumour recurrence in comparison with the control group (57.7%). This was better than the results of Kang *et al*, who reported recurrence in 40.4% of patients (19/40) treated with adjuvant imatinib for 2 years at a median follow-up of 56.7 months.¹⁹

In fact, the recurrence rates in some older studies were even better. In a pilot study, Nilsson *et al* reported that only 1 of 23 patients treated with adjuvant imatinib developed recurrent disease during a mean follow-up period of 40 months (range: 18–62 months), in contrast to 67% (32/48) in a historical control.¹¹ In the ACOSOG Z9001 trial, DeMatteo *et al* reported that 30 (8%) of the 359 patients in the imatinib group experienced a relapse at median of 19.7 months following surgery (range: 0–56.4 months) whereas 70 (20%) of the 354 patients in the placebo group suffered this adverse event.¹² Apart from the longer follow-up period and smaller sample size, this discrepancy in outcomes might also be a reflection of the fact that colorectal GISTs have a higher risk of recurrence than those at other sites.

Owing to the retrospective study design, the distribution of some prognostic factors such as mitotic count and risk stratification were found to be disproportionate across the study arms, with more at-risk patients being included in the imatinib group than in the control group. A substantial improvement of RFS and OS was nevertheless observed, demonstrating the significant role of imatinib in the management of GISTs.

Despite this, the actual benefits from adjuvant therapy might be underestimated. In addition, patients included in previous studies were at high risk of tumour recurrence, having large tumours or a high mitotic count.^{11,12,20,21} Tumour size was considered an important factor when determining RFS, with the greatest benefits being observed in those with very large tumours (≥ 10 cm).¹² However, only half of the patients treated with imatinib in our series had a tumour size of >10 cm. Besides the heterogeneity of the study design, this might also contribute to why patients in our series appeared to benefit less from adjuvant therapy than in previous studies.

Study limitations

Our data were retrospective and this report is therefore subject to errors that commonly arise from such analyses. First, information on the side effects attributable to imatinib therapy was not well recorded and so it was not possible to evaluate the related adverse events. The most frequently reported adverse reactions were diarrhoea, fatigue, nausea, oedema, decreased haemoglobin levels, rash, vomiting and abdominal pain, which seemed to be non-specific and not life threatening.¹²

Second, although promising as an adjuvant therapy, optimal doses and duration of adjuvant treatment have yet to be established. In the present study, all patients were treated with a daily dose of 400mg with a median duration of 14 months. Some studies suggest there might be an increased benefit to higher doses of imatinib (400mg twice daily) or prolonged treatment duration for high risk patients.^{22,23} Further analysis of data from the adjuvant studies should provide an additional insight on this topic.

Conclusions

Our retrospective study highlights the efficacy of adjuvant imatinib therapy in decreasing the risk of tumour occurrence and prolonging the OS time in colorectal patients. Postoperative imatinib administration should be an essential part of clinical practice guidelines for the management of colorectal GISTs, not only an alternative treatment option.

Acknowledgements

The authors would like to express their sincere gratitude to the medical staff at the Department of General Surgery for their kind assistance in data acquisition.

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