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Recurrent Gastrointestinal Stromal Tumours Treatment: A Comparative Study

SHERIF EL PRINCE SAYED, M.D.*; OSAMA ABDULLAH ABDULRAHEEM, M.D.** and IBRAHIM EL ZAYAT, M.D.***

The Department of General Surgery, Faculty of Medicine, Bani Swif, Sohag** and Aswan*** Universities*

Abstract

Background: In recurrent GIST whether to consider surgery or to continue on imatinib is still an open question.

Aim of Study: To study the role of surgery to treat residual disease versus imatinib mesylate (IM) only to improve progression free survival (PFS) and overall survival in recurrent gastrointestinal stromal tumour (GIST) patients who are responding to imatinib mesylate.

Patients and Methods: Three to eight months after starting IM for recurrent GISTs, eligible patients were randomised to two groups: Group A (surgery for residual disease then IM) and Group B (IM treatment alone). In Group A (15 pts), surgery was performed to remove residual macroscopic lesions as completely as possible, and IM treatment continued after surgery. In Group B (15 pts), IM was given alone at a dose of 400mg per day until disease progression. The primary endpoint was progression free survival PFS measured from the date IM started.

Results: Thirty patients were enrolled in Aswan University Hospital between January 2018 to January 2021. 2-year PFS was 80% in the surgery group and 53.3% in the IM-alone group (p=0.121). Median overall survival (mOS) was 73.3% in the surgery group and 40% in patients with IM-alone group (p=0.065).

Conclusions: Excision of recurrent GIST may improve the outcome of recurrent GIST patients who respond to IM.

Key Words: *Gastrointestinal stromal tumours – Surgery – Imatinib.*

Introduction

RECURRENCE of GIST soccured in around fifty percent of patients, in spite of total excision. For recurrent gastrointestinal stromal tumours, the average survival period was 6-18 months **[1,2]**.

Therapy with imatinib mesylate (IM) has improved GISTs treatment and survival **[3,4]**. Nowadays, IM is the treatment of choice for recurrent gastrointestinal stromal tumors and its results regarding progression free survival (PFS) and average survival has been strongly approved **[5-10]**. Unfortunetely, after first response, a secondary resistance to IM occurs at a median time of 2 years from starting the drug **[10,16]**. Average survival of recurrent gastrointestinal stromal tumours patients taking imatinib is five years **[10]**.

Pitfall of imatinib is the occurrence of secondary resistance **[11,12]**. Role of surgery combined with IM in the treatment of GISTs patients is debatable **[13-15]**. Secondary resistance happens due to many reasons, including the occurrence of secondary mutations, that produce IM resistance **[16]**.

Aim of the study:

Given the resistance of IM in patients with recurrent GIST, multimodality therapeutic choices are currently being explored. A reason for excision of recurrence upon responding to imatinib is that a decrease of tumour load might reduce secondary resistance. Comparing the two options surgery plus Imatinib versus Imatinib only is our issue.

Patients and Methods

Patients:

Pathologically confirmed, recurrent gastrointestinal stromal tumours were eligible.

Inclusion criteria:

1- Surgically resectable recurrent disease after radiological assessment with CT/MRI.
2- Treatment with imatinib administered for 3-8 months with partial regression (PR) or stable disease (SD) by (CT)/(MRI).
3- Absence of metastases.

Correspondence to: Dr. Sherif El Prince Sayed, The Department of General Surgery, Faculty of Medicine, Bani Swif University

Patients were excluded if tumour progression occurred on Imitinib before randomization.

Study design:

This was a randomized controlled study, performed in Aswan University Hospital between January 2018 to January 2021. Thirty patients were followed within 3 to 8 months of imatinib treatment at a dosage of 400mg per day for recurrent tumor, assessment was done based on CT/MRI within two weeks before randomisation. The patients were assessed and defined as, PR (partial response) and SD (stable) in comparison to the first disease, before imatinib onset within the same duration. Cases with operable recurrent tumour after assessment were randomised to 2 groups using group A 15 patients (surgery for recurrent tumour plus imatinib) and group B 15 patients (imatinib only). In group B (imatinib only), imatinib was taken orally at 400mg per day until disease pro-gression. In group A (surgery for recurrent tumour), surgery was done as early as we can. Imatinib was given after operation soon as we can.

Follow-up:

The progression free survival (PFS), calculated from starting imatinib to the date of relapse. Progression of tumour (local or distant) was considered a relapse. Overall survival calculated from the day of starting imatinib till death. In the surgery group, complications of surgery will also be reported. For all cases, follow-up were performed every 6 months until relapse. Surgical evaluation was performed on all patients with CT/MRI scan before operations. Surgeries for patients in group A aiming to achieve R0 (complete excision).

Ethical committee approval was taken.

Statistical analysis:

Data were collected, coded, revised and entered to the Statistical Package for Social Science (IBM SPSS) version 20. The data were presented as number and percentages for the qualitative data, mean, standard deviations and ranges for the quantitative data with parametric distribution and median with inter quartile range (IQR) for the quantitative data with non-parametric distribution.

Chi-square test was used in the comparison between two groups with qualitative data and Fisher exact test was used instead of the Chi-square test when the expected count in any cell found less than 5.

Independent *t*-test was used in the comparison between two groups with quantitative data and parametric distribution and Mann-Whitney test was used in the comparison between two groups with quantitative data and non parametric distribution.

The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the *p*-value was considered significant as the following:

- $p>0.05$: Non significant (NS).
- $p<0.05$: Significant (S).
- $p<0.01$: Highly significant (HS).

Results

Table (1): Demographic data among studied groups.

	Group A (Surgery and glivec)		Group B (Glivec)		Independent *t*-test	
					t	*p*-value
Age:						
Mean ± SD	59.14±3.14		60.87±3.68		1.385	0.177
Range	40-65		50-70			
Sex:	No.	%	No.	%	Chi square test	
Female	5	33.3	5	33.3	1.222	0.268
Male	10	66.7	10	66.7		

Table (2): Tumour criteria among studied groups.

	Group A (Surgery & glivec)		Group B (Glivec)		Independent *t*-test	
	No.	%	No.	%	X^2	*p*-value
Organ:						
Stomach	6	40.0	5	33.3	0.602	0.7400
Intestine	4	26.7	6	40.0		
Rectum	5	33.3	4	26.7		
Duration from first surgery to recurrence:						
<24 months	10	66.7	9	60.0	0.144	0.704
>24 months	5	33.3	6	40.0		
Response to glivec:						
Partial remission	9	60.0	5	33.3	2.143	0.143
Stable disease	6	40.0	10	66.7		
	Mean ±SD		Mean ± SD		Independent *t*-test	
Glivec duration before randomization (months)	7	0.1	8	0.1	27.386	0.001

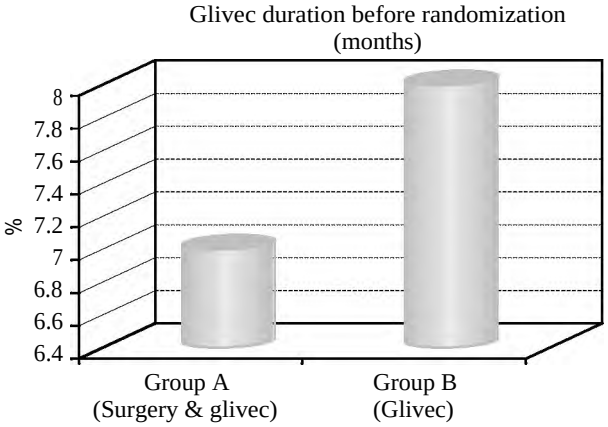

Fig. (1): Duration of glivec treatment before randomization.

Table (3): Progression free survival PFS, Overall survival, among studied groups.

	Group A (Surgery & glivec)		Group B (Glivec)		Chi square test	
	No.	%	No.	%	X^2	*p*-value
- Progression free survival PFS (2 years)	12	80	8	53.3	2.4	0.121
- Overall survival (3 years)	11	73.3	6	40	3.394	0.065

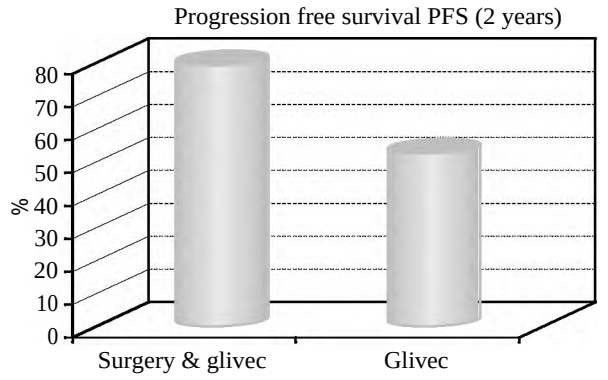

Fig. (2): Progression free survival (PFS) 2 years.

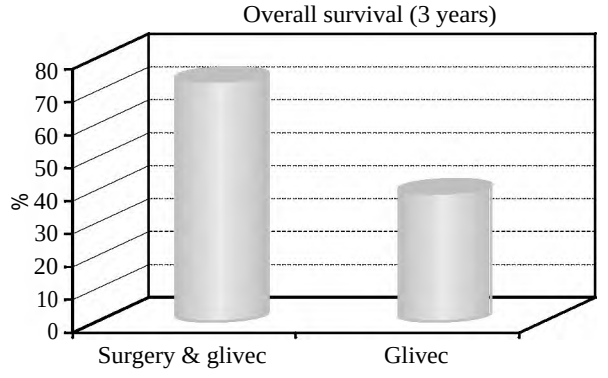

Fig. (3): Overall survival (3 years)

Table (4): Surgery criteria among studied groups.

	Group A (Surgery & glivec)	
	No.	%
Surgery criteria:		
R0 (complete resection)	10	66.7
R1	5	33.3

Table (5): Morbidity (bleeding, infection and ileus) among surgery criteria.

	R0 (No.=10)		R1 (No.=5)		Chi square test
	No.	%	No.	%	*p*-value
Bleeding:					
400 ml	4	40.0	0	0.0	0.098
600 ml	0	0.0	2	40.0	0.031
Infection	3	30.0	2	40.0	0.698
Ileus	1	10.0	2	40.0	0.170

Discussion

Excision of recurrence with Imatinib may be the treatment of choice for longer life in recurrent GIST s. When IM has decreased tumour volumes for patients with recurrent gastrointestinal stromal tumours, surgery may help to remove the recurrent disease before secondary resistance occurs, or to stop disease relapse by removing resistant clones **[17,18]**. Whether to operate in patients whose show response to IM to continueon it is still a question. No data available to approve this. Partial response or stabilisation occur in nearly 80% of patients with recurrent GIST s with IM treatment. A large percent of patients receiving IM experienced relapse **[20,21]**. In our results partial remissions occur in 60% of surgery group and 33.3% of IM group before randomisation and stable disease in 40% of surgery group and 66,7 of IM group.

In our study better survival was shown among patients who were operated than those who took imatinib only. IM resistance is the cause of the short-term efficacy of the therapy. This is due to many reasons, mainly pharmacokinetic changes and mutations that become apparent after long treatment duration **[19]**. This fact provides a justification for the usefulness of surgery as treatment of recurrent GIST. Having different mode of action than do 'conventional' cytotoxic drugs, it is obvious that inspite good clinical result, IM does not show full pathological response **[22]**. Many previous studies during the last decade have measured the value of doing surgery with imatinib **[23-28]**. A

retrospective study done by Raut of 69 patients with recurrent GIST s for whom surgery was done-then receiving IM and reported that 12 months (PFS) was 80%, 33% and 0% for patients with stable disease, limited progression and generalised progression, respectively [29].

Another studies, on a small scale, have concluded a better survival for patients undergoing excision of recurrence following IM therapy [30-34]. PFS and overall survival were longer for patients in our study operated then received imatinib it was 80% and 73.3% respectively compared to IM group which was 53.3% and 40% respectively. In a recent trial evaluating IM therapyalone for recurrent gastrointestinal stromal tumours progression free survival was shorter [10]. The mean age of patients in our study in both groups were comparable 59.14 and 60.87 respectively. This may show that the better survival in this subgroup of patients who received surgery is an effect of the combination of imatinib and surgery, rather than a selection of better patients that would have had the same outcome even with imatinib alone. Blay et al., [35] in his study found a 2-year PFS of <30% from randomization, from one year after taking IM without surgery.

In our study the severity of surgical complications was low in the form of less than 600ml bleeding compensated during surgery and controllable infection in 5 cases and ileus in 20% managed conservatively. The rate and severity of complications are within the range of other studies [32].

The cases with recurrent GIST tumours showing no response or partial response on imatinib have longer overall survival after excision of recurrence. Wang et al., Concluded that the efficacy of post-operative imatinib for recurrent patients with follow-up five years progression free survival (PFS) and overall survival were 30% and 68% respectively [36].

The aim of operation is to excise the recurrence with the least complications. Many studies concluded how operating on these patients safe and applicable [37,38]. In our study, complete resection was achieved in 66.7% of cases. Surgical morbidity occured in patients who underwent resection were controllable and none needed further surgery. It is indicated that surgical resection of residual disease for recurrent GISTs responding to IM is feasible and safe. However, surgery for residual disease is not a simple procedure. According to our data, the mean volume of blood loss was 600ml, meaning that the surgery should be taken carefully and by specialised surgeon.

In conclusion:

This study concluded that surgical excision of recurrence followed by Imatinib may increase the (PFS) and overall survival of gastrointestinal stromal tumours patients who showrecurrence (after regression of tumour by imatinib or even stabilisation) than Imatinib alone. Excision of recurrence is feasible and with limited morbidity.

Conflict of interest statement:

None declared.

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علاج أورام الأنسجة الرخوة للجهاز الهضمى المرتجع : دراسة مقارنة

ورم الأنسجة الرخوة المرتجع للجهاز الهضمى كان يعالج الـ imatinib ولا يوجد ما يثبت دور الجراحة قبل الدواء.

حدوث مقاومة وطفرات للورم أثناء العلاج جعل التفكير فى علاج مساعد للدواء للحصول على نتائج أفضل.

تم عمل تصنيف للمرضى الذين يعانون من ارتجاع للورم مجموعة أ : تم عمل استئصال للورم المرتجع لخمسة عشرة حالة بعد العلاج بالدواء.

ثم استكمال العلاج بالدواء مجموعة ب : استكمال العلاج بالدواء لخمسة عشرة حالة لحين حدوث انتكاسة فى صورة ارتجاع موضعى أو انتشار وحساب المدة وعدد الأشخاص الذين حدوث لهم انتكاسة على مدار عامين ثم حساب المدة العمرية للمرضى على مدار ثلاث سنوات. الأعمار السنية للمرضى الثلاثون متقاربة. العمليات التى أجريت لم يكن منها مضاعفات شديدة.

استجابة المرضى للدواء قبل التصنيف للعلاج كانت ياما استجابة جزئية أو ثبات.

العمليات نتج عنها استئصال كلى للأورام فى عشر حالات أو جزئى فى خمس حالات.

الدراسة المقارنة أثبتت أن استئصال الأورام المرتجعة بعد العلاج لفترة ثم معاودة العلاج تأتى بنتائج أفضل من حيث فترة عدم ارتجاع الورم ومن حيث المدة العمرية للمرضى وذلك بالمقارنة بالعلاج بالدواء دون الجراحة.

ونظرى للتقارب ففى الأعمار السنية بين المرضى فى المجموعتين فهذا يثبت عدم وجود أفضلية لمجموعة عن الأخرى وبالتالى صحة النتائج الجراحات التى أجريت لم يحدث معها مضاعفات شديدة مما يجعلها ممكنة ولكن نظراً لأن الورم المرتجع يكون أصعب جراحياً مما قد يحدث مضاعفات أثناء العملية من نزيف وغيرة لذلك يجب إجراء العمليات بواسطة جراح أورام متخصص.

تقييم المرضى قبل إجراء العمليات أو بدأ العلاج يكون بالأشعة المقطعية أو الرنين.

النقطة الفاصلة فى الدراسة هو حدوث انتكاسة موضعية أو انتشار.