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Original Article

PHASE II TRIAL OF IMATINIB IN METASTATIC OR UNRESECTABLE GASTROINTESTINAL STROMAL TUMORS, NEMROCK EXPERIENCE.

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ABSTRACT

Aim of the Work: Imatinib was approved for treatment of metastatic or unresectable gastrointestinal stromal tumor (GISTs) in February 2002. Accordingly we study the role of imatinib in Egyptian GISTs patients.

Patients and Methods: Fourteen Patients with a histologically confirmed, unresectable or metastatic gastrointestinal stromal tumor that expressed CD117 (a marker of KIT-receptor tyrosine kinase) were eligible for the study.

Results: fourty three percent of the patients had a partial response, while onlyone patient had achieved complete response (7%), 35.71% of patients had stable disease, and disease progression was noted in 14% percent of patients between one and three months after study entry. Imatinib was very safe drug, the most common side effect was mild to moderate (grade 1-2) edema or fluid retention (in 64.2% of patients). Nausea was seen in 50% of patients, diarrhea in 35.7%, rash related to the drug in two patients (14.2%).

Conclusion: Imatinib mesylate is an active drug in advanced unresectable or metastatic GISTs. And it is a very safe drug.

Key Words: Gastrointestinal stromal tumors, GIST, imatinib, glivec.

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) constitute the largest group of mesenchymal tumor of the gastrointestinal tract. They originate from the interstitial cell of Cajal, or from a primitive stem cell that differentiates towards both the interstitial cell of Cajal and smooth muscle phenotype.[1]

Approximately 85% of GISTs express the cell-surface trans-membrane receptor KIT that has tyrosine kinase activity, the ligand for KIT is a growth factor called the stem cell factor. There are frequent gain-offunction mutations of KIT in gastrointestinal stromal tumors. These mutations result in the constitutive activation of KIT signaling, which leads to uncontrolled cell proliferation and resistance to apoptosis.[2]

Before 2002, surgery was the only effective treatment for GISTs. But in approximately 50% of patients, complete resection was not possible and median survival ranged from 10 months to 23 months. In a recently reported series, the response rate to doxorubicin was less than 5%.

The effectiveness of radiation therapy for this disease has not been proved[3,4]. Imatinib mesylate (formerly STI571, now referred to as Gleevec in the United States and Glivec in Europe Novartis) is a selective inhibitor ofcertain protein tyrosine kinases: The intracellular ABL kinase, thechimeric BCR-ABL fusion oncoprotein of chronic myeloid leukemia, the transmembrane receptor KIT, and the platelet-derived growth factor receptors[5]. In 2002, a large multicenter trial of imatinib for patients with metastatic GIST demonstrated partial responses in 54%, stable disease in 28%, and disease progression in 14%[6]. Imatinib was approved for treatment of metastatic or unresectable GISTs in February 2002.[7]

With these recent changes in the management of GISTs, it is critical to reassess the role of imatinib in GISTs Egyptian patients. We present a single center experience of imatinib in GISTs Egyptian patients.

Patients and methods: The current study was conducted in Kasr El-Aini Center of Oncology and Nuclear Medicine (NEMROCK), Cairo University and Department of Clinical Oncology and Nuclear Medicine, Monofia University during the period between January, 2005 through January 2006 where 14 patients with both

pathologic and immuno-histochemical proven Metastatic and/or un-resectable Gastro-intestinal Stromal Tumor (GIST) to assess the efficacy as well as tolerability profiles of imatinib mesylate, (Phase II Trial). Inclusion Criteria included[1]. At least one lesion with no prior targeting via any ablative procedure[2]. Performance status scale of three or lower according to Eastern Cooperative Oncology Group ECOG[3]. Adequate hematological, hepato-renal and cardiac profiles[4]. Prior chemotherapy was not considered as a violation to protocol provided that last exposure was more than four weeks from initiation of imatinib therapy[5]. No associated co-morbid Oncologic event which might contribute to shortened life expectancy as brain deposits or massive pulmonary involvement mandating intubation or assisted ventilation[6]. Prior palliative Debulking or life saving surgeries were allowed. Drug Administration: Enrolled patients were instructed to have 400mg once daily with meals and plenty of plain water, and to be repeated daily with no of days. Assessment of Response and Toxicity: All patients were subjected to full history taking including detailed prior therapies, through clinical examination as well as full laboratory investigations, chest and abdominopelvic radiologic imaging including CT-Scanning and/or Magnetic Resonant Imaging for precise assessment of tumor burden. PET scanning was not planned to be a part of the investigation panel due to administrative un-certainties and extra-cost, although performed in one patient.

The response to treatment was evaluated every two months during the first 6 months, then every 6 months unless indicated according to clinical judgment. Assessment was addressed according to Southwest Oncology Group (SWOG) Criteria.[8]

Toxicities were graded and documented on monthly basis according to National Cancer Institute Common Toxicity Criteria version 2.0.[9]

RESULTS

The current phase II study had recruited fourteen patients with established diagnosis of recurrent, residual and/or metastatic GISTs during the period of January, 2005 through January 2006 and continued to be followed up for 6 months after recruitment of the last patient. Characteristics of the patients are summarized in table 1. The duration of follow up ranged from 6-18 months with a median value of 11.5 months (SD + 3.992); (95% CI = 2.31).

Only one patient (14%) had achieved a complete response. Overall, 43% of the patients had a partial response as shown in table 2. All these partial responses were confirmed by repeated imaging at least 28 days later. An additional 35.7% of patients had stable disease, and disease progression was encountered in 13.6% of patients between one and three months after study entry. The median duration of response has not been reached. Time to treatment failure and overall survival are shown in figure 1 and 2.

Table 1: Patients characteristics.

Characteristic	Value
Age	
Median	52 years (SD + 9.04)
Range	32 70
Sex	
Male	8 (57.14 %)
Female	6 (42.85 %)
ECOG status	
Grade (0)	4 (28.57 %)
Grade (1)	5 (35.71 %)
Grade (2)	4 (28.57 %)
Grade (3)	1 (7.14 %)
Site of tumors	
Stomach	5 (35.71 %)
Small intestine	5 (35.71 %)
Liver	7 (50 %)
Peritoneum	9 (64.28 %)
lung	3 (21.42 %)
Previous treatment	
Surgery	10 (71.42 %)
Chemotherapy	2 (14.28 %)
Radiotherapy	1 (7.14 %)

Table 2: Response rate to imatinib in GISTs patients.

Response	Rate
Complete response	1 (7%)
Partial response	6 (43 %)
Stable disease	5 (35.71 %)
Progressive disease	2 (14.28 %)

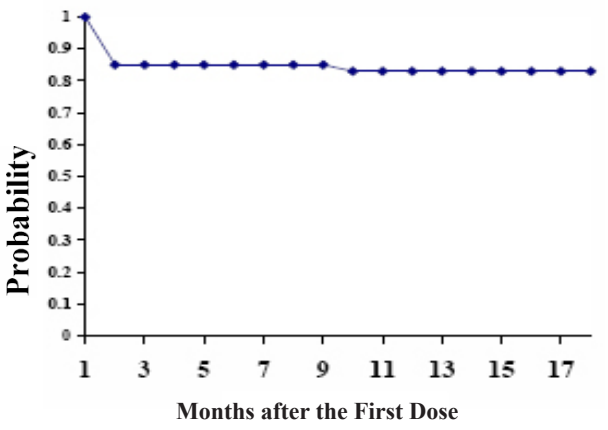

Fig. 1: Kaplan-Meier estimates of time to treatment failure.

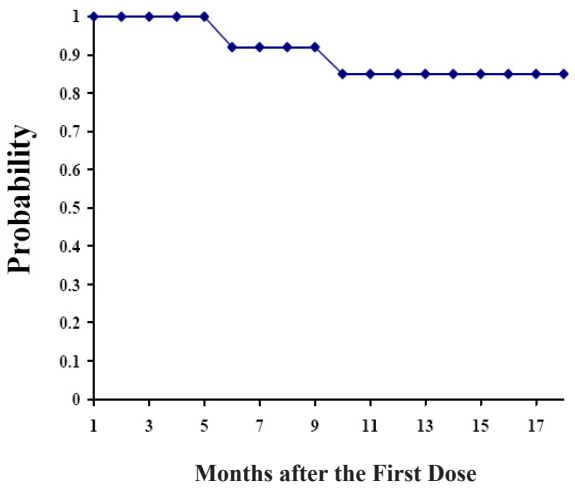

Fig 2: Kaplan-Meier estimates of overall survival.

Imatinib was very safe drug, the most common side effect was mild to moderate (grade 1-2) edema or fluid retention (in 64.2% of patients) and it was most frequently periorbital and leg. Nausea was seen in 50% of patients, diarrhea in 35.7 percent, rash related to the drug in two patients (14.2%). There was no gastrointestinal or intraabdominal hemorrhages.

DISCUSSION

Imatinib therapy as first-line systemic treatment produces disease regression or stabilization in approximately 80% of patients with advanced GISTS. Our results regarding the response rate corroborate the result obtained with imatinib in multicenter phase II trial which achieved 7% complete response, 43% partial response, 27.9% stable disease and 13.6 progressive disease.

Although our results indicate that imatinib is effective for many patients with advanced gastrointestinal stromal tumors, low rate of complete response and resistance of tumors to single-agent therapy is common, in 14% of our patients. The resistance is multifactorial. First it may be due to various genetic locations of the c-Kit mutation which is directly correlated to the tumor responsiveness (e.g. exon 11 mutations have better response rate and survival than either exon 9 mutations or wildtype c-Kit mutations)[10]. Or it may be due to evolution of resistant clones, as in secondary drug resistance which is characterized by the acquisition of additional activating KIT or PDGFRA mutations in tumor clones, rendering imatinib ineffective.[11]

Treatment with imatinib was generally well tolerated; most events were mild to moderate in severity. Edema, nausea, diarrhea and headache were the frequently reported adverse events.[6,7,12]

We are waiting for an answer to many questions, when to stop the drug, is surgery of value after partial response, the role of adjuvant imatinib after surgical removal of the lesion, how to augment the activity of imatinib.

We need many randomized clinical trials to answer the previous questions.

CONCLUSION

Imatinib mesylate is a useful drug in advanced unresectable ormetastatic GISTs, Objective response was achieved in 50% of cases. Inaddition, another 35% have stabilized disease. Imitinib was well tolerated in Egyptian GISTs patients.

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