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Background: Understanding the molecular pathogenesis of gastrointestinal stromal tumors (GIST) has led to targeted therapy using imatinib mesylate (IM). This retrospective series summarizes our short-term experience with 50 cases of GIST.

Methods: Case records of patients with GIST were analyzed. Tumor size, response to imatinib, and adverse events were evaluated every 3 months.

Results: The median age was 50 years (range 28-73). Stomach was the most common site (n=15). Thirty (60%) patients had complete resection of tumor with median progression free survival (PFS) of 12 months. The difference in PFS between intermediate and high risk groups was significant for patients who underwent resection (p=0.016). Thirty-five patients with advanced disease were administered IM 400 mg daily, and complete response was noted in 4 (11.8%); 13 (38.2%) each had partial response and stable disease, and 5 (14.8%) had progressive disease. Responses were not different in groups based on sex, site of primary tumor and number of metastatic sites. At a median follow up of 10 months, 72% patients continue to maintain response.

Conclusions: This short-term study in patients with GIST describes response to therapy with imatinib in these patients.

Methods

Fifty patients who were diagnosed to have GIST during the period from January 2004 to April 2007 on the basis of biopsy from either primary or metastatic sites were included in this analysis. Patients whose diagnosis was made on fine needle aspiration cytology were excluded. The diagnosis of GIST was based on light microscopic features and membrane positivity for CD 117 by immunohistochemistry (IHC). Extended panel of IHC markers were done if necessary. IHC for platelet derived growth factor (PDGF) was not done for the CD117-negative patients. The case records of these patients were reviewed retrospectively and data on the following parameters were retrieved: age, sex, site of primary and metastasis, histopathologic subtype, nature of treatment given, response to imatinib and adverse events. Patients who had curative surgery were stratified into low, intermediate and high-risk groups based on the size of GIST.
primary tumor and number of mitoses per 50 high power fields. At baseline, ultrasonography of abdomen (USG), chest radiograph, or contrast-enhanced computed tomography (CECT) were done, as appropriate. All patients were on 3-monthly follow up with clinical examination and USG and/or CECT. No routine blood tests were performed during follow up unless clinically warranted.

Patients, who had tumor recurrence after curative surgery or were diagnosed as de novo locally advanced inoperable disease or metastases, were started on oral imatinib mesylate 400 mg once daily. They were not on any drugs that had interactions with IM or other non-prescription drugs. Only patients who had completed at least 3 months of therapy at the time of analysis were eligible for response evaluation. Response to IM was defined as follows: Complete response (CR) - complete disappearance of disease at all sites and no new lesions; partial response (PR) - decrease of 30% in the sum of the single largest diameters of all measurable lesions; stable disease (SD) - less than 30% decrease or less than 20% increase in the sum of the single largest diameters; and progressive disease (PD) - an increase in the sum of the single largest diameters by 20% or appearance of new lesions. The dose of IM was increased to 600 mg on disease progression and patients continued to be on 3-monthly follow up.

On further progression, other options including sunitinib or best supportive care were discussed. Patients were followed up until death or last hospital visit. Adverse events, if any were recorded in patients who were initiated on IM. Progression free survival (PFS) after complete resection was defined as the time from surgery to the time of clinical or radiological evidence of relapse. PFS on IM was defined as time from initiation of IM therapy to clinical or radiological evidence of progression, death or lost to follow up. Overall survival was defined as time from surgery or IM initiation to death or last follow-up.

Difference in response rates between various groups was tested by Fisher’s exact test. Differences in median PFS between intermediate and high risk groups were tested by log rank test. Kaplan Meier curves for PFS were plotted using GraphPad Prism software for Windows, Version 4, 2003.

Results

During the period from January 2004 to April 2007 there were 50 patients (33 male) with confirmed diagnosis of GIST. The median age was 50 (range 28-73) years.

Abdominal pain was the most common symptom (n=36) followed by weight loss (19) and gastrointestinal bleed (16). The other symptoms were vomiting (11), abdominal distension (14), change in bowel habit, abdominal mass and dyspepsia in 10 patients each, fatigue (8) and anorexia (7).

The anatomic sites of primary tumor stomach (n=15), jejunum (9), large bowel (8), ileum (7), mesentery (5), and duodenum and pancreas (2 each). The primary site could not be made out clearly from the case records in 2 patients. The median size of the primary tumor was 10.5 cm (range 3-27 cm). The histopathological subtype of GIST was sarcomatoid in 33 (66%), epitheloid in 11 (22%) and mixed in 7 (14%) patients.

Laparotomy was done in 42 (84%) patients, and 30 (60%) had complete resection while 12 (24%) had only a biopsy. Based on the size of the primary and the number of mitoses, 3 (10%), 14 (47%) and 13 (43%) patients were classified as low, intermediate and high-risk category, respectively. After complete resection, the median PFS was 12 months (range, 3-43 months); by 43 months all patients with complete resection had evidence of disease progression (Fig 1).

The median PFS of patients in the intermediate risk group was 16.5 (3-36) months and that of the high-risk group was 6 (3-43) months. The difference in the median PFS between the intermediate and high-risk groups was significant (p=0.0161; HR [95% CI] 0.3522; Fig 2). The median PFS of 3 patients in the low risk group had not been reached. Twelve patients developed recurrence of disease in the peritoneum, and 8 in the liver. Two patients each had local
and lymph nodal relapse. At 20 months (range, 3-54 months) follow up, 85% of patients who underwent complete resection were alive.

Thirty seven patients relapsed after resection or presented with de novo inoperable disease. The sites of metastasis or recurrence were as follows: peritoneum - 23 (62%), liver- 17 (46%), lymph nodes - 8 (21%), local recurrence – 3 (8%) and lung - 1 (2%). Twenty (54%) patients had disease in more than one site.

Of the 37 patients with relapsed or metastatic disease, one underwent surgery and one did not take any therapy. Thirty five patients were initiated on IM of which one was not evaluable for response. Of 34 evaluable patients, complete response was achieved in 4 (11.8%), 13 (38.2%) each had partial response or stable disease, and 4 (11.8%) had progressive disease. There was at least a CR, PR or SD in 30 (88.2%) patients. The difference in response between males and females (30 [90.4%] vs 13 [76.9%]), single versus multiple sites of metastasis (12 [78.5%] vs 13 [80%]), site of primary tumor (stomach versus small bowel primary (13 [90%] vs 15 [83.3%]) and patients with de novo metastasis versus those who recurred after surgery (11 [68.2%] and 14 [93.2%]) was not significant.

Facial or pedal edema (n=17) and hypo or hyperpigmentation of the skin (17) were the most common adverse events. Other adverse events were musculoskeletal pain (11), alteration in liver biochemistry (3), constipation (2), oral ulcers (2), diarrhea (1), muscle cramps (1), and burning feet (1). The drug was not discontinued in any patient due to adverse events.

At a median of 10 months (range, 1-36 months) for all patients on imatinib, 24 (72%) continue to be on follow up without progression (Fig 3). Twelve patients progressed on imatinib of which one was lost to follow up. Five of 11 patients in whom the dose was increased to 600-800 mg/day had stable disease and 6 patients had no response. One patient who received sunitinib 50 mg daily had progressive disease in 3 months.

Discussion

Our analysis of 50 patients with GIST confirmed the significance of risk stratification for patients with resected tumors and the favorable response rates with imatinib mesylate for those with inoperable or metastatic disease. Our study consisted of a heterogeneous group of patients - those who presented with localized resectable disease, de novo metastatic disease and those who relapsed after complete resection of their tumors. The pitfall of this analysis is that being a retrospective study, 40% of evaluable patients had USG as the method of tumor evaluation, which is sub-optimal and could overestimate response rates.

The median age of patients was 50 years, which is a decade lower than that reported in the west.1,12,13 Most studies report a slight male preponderance compared to the ratio of 2:1 in our study. Most patients with GIST (70%) have non-specific symptoms at presentation;1 20% are detected incidentally and 10% at autopsy.3 Abdominal pain was the most common symptom in our series. Although GISTS tend to grow extraluminally, erosion into the lumen may cause a GI bleed, which occurred in about a third of our patients.

The stomach was the most common site for the primary tumor in our patients, consistent with some
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 reports, although other authors have reported small bowel as the most common site. Extra gastrointestinal stromal tumors arise in the soft tissues of the gastrointestinal system, and are infrequent. These tumors are pathologically similar to their gastrointestinal counterparts with 100% positivity for immunostaining with CD 117 and treated similar to GISTs. These occurred in 10%, which included mesentery and omentum.

Although laparotomy was done in 82% of patients, complete resection could be done in only 60% of them. The median PFS for patients with complete resection was 12 months; this figure is lower than the 18-24 months reported in western literature. In our series, 90% belonged to the intermediate and high-risk groups suggesting late presentation and aggressive biologic behavior, which may account for the inferior PFS. As reported earlier, the difference in median PFS between the intermediate and high-risk groups was significant.

Of all patients with metastatic/inoperable disease, 62% and 46% had peritoneal and liver involvement, respectively. Western literature reports liver as the most common site in 70% followed by peritoneum. Lymph nodes as a site of metastasis is extremely rare (<2%); 21% of our patients had lymph node disease.

Of the 34 patients who received IM, there was at least a CR, PR or SD in 88.2% patients. Most western studies report a PR of 41%-66% and SD of 17%-31% amounting to a PR+SD rate of 80-90%. Complete responses are rare and amount for around 5%. Ultrasound is a poor method to evaluate peritoneal disease, and it may have underestimated CRs in our series. Currently, response criteria used for GIST are far from ideal and are evolving.

Clinical factors predictive of responses have not been reported in most trials except in one study where higher hemoglobin predicted for better responses. The only factor that has consistently been predictive of response is the site of kinase domain mutation. In patients with GISTs harboring exon 11 KIT mutations, the partial response rate (PR) was 83.5%, whereas in those with an exon 9 KIT mutation or no detectable mutation of KIT or PDGFRα the PR rates were 47.8% and none, respectively. No mutation studies were done on our patients.

Facial or pedal edema and hypo or hyper pigmentation of the skin were the most common adverse events that occurred in almost half of our patients. No routine blood tests were performed unless clinically warranted. Hence, there may be underreporting of hematological and biochemistry related adverse events in our study. Western studies report a higher incidence of edema and nausea but lower incidence of skin rash.

The 5-year survival for patients with resected GIST is 50%. There are no large prospective studies that have evaluated the outcome of patients with primary GIST. For patients on IM, the 1-year PFS of 76% in our patients is comparable with that of 65%-82% reported in other studies. As only 12 out of 35 patients had disease progression, we did not perform multivariate analysis for prognostic factors. Male gender, GIST from bowel origin, baseline low hemoglobin and high neutrophil counts are known to predict for worse progression free survivals.

Our study confirms the short term efficacy and safety of IM in patients with inoperable and metastatic GIST. None of the clinical factors predict for response. The progression free survivals at one year are favorable.

References

Gastrointestinal stromal tumors

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