ORIGINAL ARTICLE

Imatinib Mesylate in the Treatment of Chronic Myeloid Leukemia: A Local Experience

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Summary

This study was done to assess the overall response rate of imatinib mesylate in local patients with chronic myeloid leukaemia. A total of 69 patients were recruited with male/female ratio of 7:3. Of the 69 patients; 35% were in the chronic phase, 41% were in the accelerated phase, 17% were in blast crisis and the remaining 7% were after stem cell transplantation. Complete haematological response rates of patients in chronic phase, accelerated phase and blast crisis were 95.8%, 96.4% and 41.7% respectively. Thirty-eight percent of patients achieved complete cytogenetic response and 10% achieved partial cytogenetic response. The cytogenetic response rates were 80%, 41.7% and 18.2% in chronic, accelerated and blast crisis phase respectively ($p<0.005$). Twenty-six percent of patients developed anaemia, 13% had neutropenia and 12% had thrombocytopenia after starting on treatment. In addition, 14% of patients developed peripheral oedema, 13% complained of musculoskeletal pain, 12% had gastrointestinal side effects which include nausea, vomiting and diarrhoea, 9% had grade 1 hepatotoxicity, 7% developed skin rashes and one patient had an abnormal renal function test. Patients taking 600mg or higher dosage of imatinib had more gastrointestinal side effects. Patients who weighed less than 60kg had a much higher risk of developing anaemia. Anaemia was a negative predictor of cytogenetic response. Presenting high white blood cell counts and absence of cytogenetic response were also negative predictors of survival. Overall survival was 87%. This was affected by the different phases of disease (chronic phase was better than accelerated and blast crisis) ($p <0.001$). In conclusion, our local CML patients did well on treatment with imatinib.

Key Words: Chronic Myeloid Leukaemia, Imatinib mesylate (Glivec)

Introduction

Chronic myeloid leukaemia (CML) accounts for 15-20% of newly diagnosed cases of adult leukaemia. Philadelphia chromosome (t (9; 22)) is present in 95% of CML patients. It is a reciprocal translocation between the long arm of chromosome 9 and 22. The product of this fusion gene causes deregulation of normal signal transduction which leads to increased cell proliferation and the development of chronic myeloid leukaemia.

In the past, several modes of therapies were used to control the disease although interferon therapy did improve survival in some patients. Allogeneic stem cell transplantation remains the only curative option in eligible patients. However, allogeneic stem cell transplantation is not without its risk and transplant related mortality is relatively high. Because of the above limitations, efforts in searching for novel therapies for CML have continued for decades. Among the new drugs, imatinib mesylate is the most successful. It inhibits the tyrosine kinase family which include the

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BCR-ABL protein, platelet-derived growth factor (PDGF) receptor, and c-kit receptor. Imatinib competitively binds to the ATP-binding site of BCR-ABL and inhibits protein tyrosine phosphorylation in CML, inducing normal apoptosis in this abnormal cell line [1].

The adverse effects of imatinib are common but usually mild. The main toxicities encountered from imatinib include nausea, diarrhea, musculoskeletal symptoms (muscle cramps, arthralgia, and myalgia), oedema (central, truncal, and periorbital), skin rashes, hepatotoxicity and myelosuppression [2].

Several studies have shown good response in CML patients treated with imatinib. Cytogenetic response was achieved in more than 60%. These studies also showed an improved overall survival. A recent phase III study, (IRIS) compared imatinib to IFN-α plus cytarabine in newly diagnosed chronic phase patients[2]. After a median follow-up of 19 months, patients in the imatinib arm showed significantly better tolerability, better haematological and cytogenetic response and had a reduced time to progression. Major and complete cytogenetic responses at 18 months were 87.15% and 76.2% respectively in the imatinib arm and 34.7% and 14.5% respectively in the interferon plus cytarabine arm. However, the overall survival for both arms was not significantly different, probably due to the short follow-up period.

There is no study of efficacy and adverse effects of imatinib mesylate in our local patients. It is generally believed that these would be similar to that of Western patients. However, physical and genetic differences may influence the effects of imatinib mesylate in Asian patients. This study was initiated to look into the efficacy and adverse effects of imatinib in our patients. The secondary objective of this study is to assess clinical factors that affect the efficacy and adverse effects of imatinib.

Material and Methods

This is an observational study where all patients with chronic myeloid leukaemia (CML) on imatinib, from University Malaya Medical Centre and Subang Jaya Medical Centre were analysed. Patients' characteristics, response to imatinib and adverse effects were examined. The patients were followed-up from January 2001 to February 2005. Those who had incomplete data were excluded.

The response to imatinib was divided into haematological, cytogenetic and molecular response. A complete haematological response was defined as a white blood cell count of less than $10x10^9/l$, a platelet count of less than $450x10^9/l$ and no immature cells in peripheral blood, lasting for more than four weeks. Complete cytogenetic response was defined as the absence of Philadelphia chromosome. Partial cytogenetic response was defined as positivity of Philadelphia chromosome of 1 to 35%. Major cytogenetic response included complete and partial cytogenetic response.

Results

A total of 69 patients were recruited in this study. The patients' characteristics are shown in Table I. The haematological responses of the three different phases are showed in Table II. The differences were statistically significant with a p value of < 0.001 with chronic phase patients having the best haematological response. Twenty four patients (48%) obtained major cytogenetic response, 19 (38%) of them were in complete and the remaining 5 (10%) were in partial cytogenetic response (Table III). Similarly, chronic phase and accelerated phase patients had better major cytogenetic response compared to those patients in blast crisis. The response rates were 80%, 41.7% and 18.2% in chronic, accelerated and blast crisis phase respectively (Table III).

Presenting white cell count is a predictor of poor haematological response. Seventy percent of patients with presenting white cell count $< 300x10^9/l$ had haematological response. In those with higher count, only 30% had response. Indian patients had the highest rate of cytogenetic response (60%), compared to Chinese and Malay patients whose response rates were 53.1% and 50% respectively. However, the differences were not statistically significant. Anaemia was a negative predictor of haematological and cytogenetic responses in our patients which were both statistically significant.

The duration of cytogenetic response ranged from 1 to 41 months with a median of 13 months. Four patients had cytogenetic relapse after an initial response. The duration of response before relapse ranged from 13 to 19 months. Five patients (10%) achieved molecular response, three of them had peripheral blood stem cell transplantation before the treatment with imatinib.

The adverse effects of imatinib mesylate were mild and tolerable (Table IV); none of the adverse effects was severe enough to cause permanent discontinuation of imatinib treatment. Patients taking 600mg or higher dosage of imatinib had more gastrointestinal side effects which was statistically significant (p=0.03). Patients who were less than 60kg had a much higher risk of developing anaemia (p=0.007).

The range of survival after starting imatinib was 1 to 48 months with a median of 18 months. Survival was affected by phase of disease, presenting white blood cell count and cytogenetic response. Kaplan Meier analysis showed that the survival rate at 50 months were 100%, 90% and 40% in chronic phase, accelerated phase and blast crisis respectively (Figure 1). The overall survival for patients with white cell counts between 300- 500x10^9/l and more than 500x10^9/l were 80% and 40% at 20 months respectively (Figure 2). Patients who developed anaemia secondary to imatinib had a poorer survival rate compared to those who did not. The estimated overall survival rate at 50 months was 60% in the former and more than 90% in the latter.

Table I: Patients Characteristics

	Number	%
Ethnicity		
Chinese	46	67
Malay	12	17
Indian	11	16
Gender		
Male	48	70
Female	21	30

Table II: Overall Responses with Imatinib Mesylate

Responses	N	%
Haematologic response	60	87
Complete cytogenetic response	19	38
Partial cytogenetic response	5	10
Molecular response*	5	10

* 3 patients achieved molecular response post marrow transplant

Table III: Cytogenetic Response vs Phases of Disease

	Chronic phase	Accelerated phase	Blast crisis	P value
Major cytogenetic response	80%	41.7%	18.2%	0.05
Complete cytogenetic response	66.7%	29.2%	18.2%	-
Partial cytogenetic response	13.3%	12.5%	0%	-
Complete haematological response	95.8%	96.4%	47.7%	<0.001
Molecular response	0%	4.3%	9.5%*	

Table IV: Side Effects of Imatinib mesylate

Side effect	N	%
Anaemia	18	26
Neutropenia	9	13
Thrombocytopenia	8	12
Oedema/weight gain	10	14
Pain	9	13
GIT side effects	8	12
Grade 1 hepatotoxicity	6	9
Skin rashes	5	7
Abnormal renal function	1	1.4

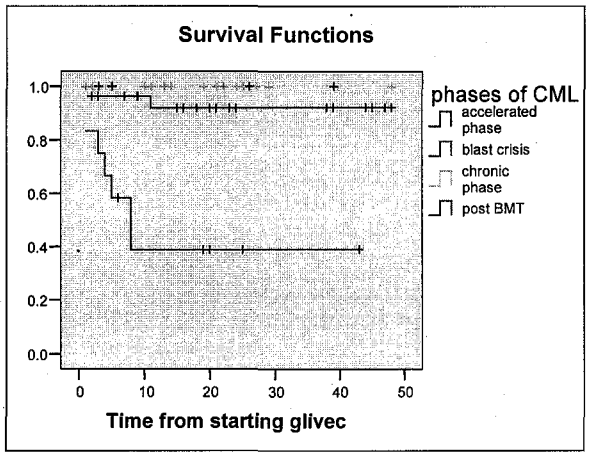

Fig 1: Influence of Phase on Survival

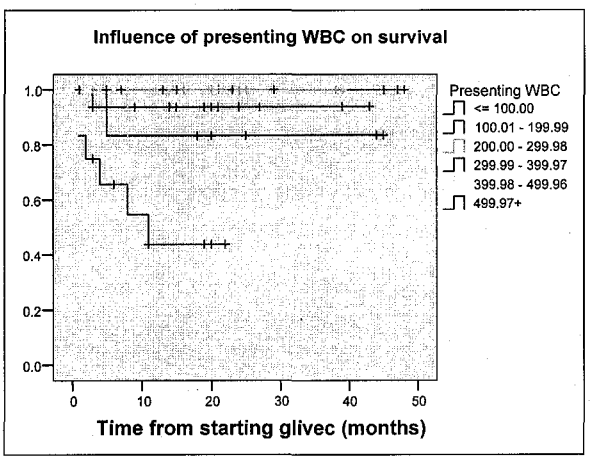

Fig 2: Influence of Presenting White Cell Count Survival

Discussion

Data from previous studies showing that imatinib mesylate has very good haematological and cytogenetic response rates was confirmed in this local study. Our study showed an excellent response rate which was comparable to that found in Western studies. It is interesting to note that our accelerated phase patients had a much higher complete haematological response of 96% versus 70-80% in other studies [1-7]. Sawyers *et al* demonstrated that the initial dose of imatinib (600 mg), haemoglobin level (at least 10g/dl), platelet count (at least 100x10^9/l) and peripheral blood blast level (below 50%) were independent predictors for a sustained complete haematological response [8]. Our analysis showed that patients had poorer complete haematological response if they had high presenting white cell counts (300x10^9/l and above) and drug-induced anaemia. The only significant factor affecting the cytogenetic response was the phase of disease. Imatinib started in the earlier phase showed a better rate of cytogenetic response. Among the different ethnic groups, Indians had the highest cytogenetic response rate, but this was not statistically significant perhaps due to our small sampling size.

The majority 40% of our patients were in the accelerated phase. This is because the Glivec International Assistance Program (GIPAP) initially was only available to those patients in the accelerated phase and blast crisis. Chronic phase patients were eligible only when they have failed or were unable to tolerate IFN-α. More newly diagnosed chronic phase patients were enrolled in the programme after imatinib was approved as first-line therapy in this group of patients in 2003.

Kantarjian et al identified that high platelet counts and percentage of Ph positivity of more than 90% prior to starting imatinib mesylate were independent adverse prognostic factors for achieving complete cytogenetic response[8]. Imatinib-induced anaemia was a predictor of poor cytogenetic response in our study. Although imatinib-induced neutropenia occurred twice as commonly in cytogenetic non-responsive patients, it was not a statistically significant negative predictor. This may be due to the relative small study sample.

Kantarjian et al also concluded that haematological resistance to IFN-α, splenomegaly and the lack of any cytogenetic response after three months of therapy were independent poor prognosticators [9]. Our study showed that presenting white cell count, the lack of cytogenetic response, imatinib-induced anaemia and advanced phase of disease were the factors which predict poor prognosis. Patients who had white cell counts of more than 500x10^9/l had a poorer survival rate. Lihui Wang *et al* concluded that occurrence of peripheral blood cytopaenias was sufficiently severe to interrupt therapy was unrelated to progression-free survival [10]. In contrast, Marin *et al* found that patients who developed neutropenia had poorer prognosis[11]. Our study revealed that imatinib-induced anaemia was an indicator of poor survival. Only 60% of imatinib-induced anaemic patients survived at 20 months

compared to 90% of patients who were not anaemic. In contrast, neutropenia and thrombocytopenia induced by imatinib did not appear to influence the survival rate in our patients. O` Dwyer *et al* reported major differences in treatment outcomes of imatinib therapy in terms of degree of cytogenetic response at three or six months [12]. The IRIS trial demonstrated there was significant difference in the progression-free survival by the 12-month response to imatinib mesylate. Those who did not achieve complete cytogenetic response by 12 months had a 80% progression-free survival rate. A 3-log or greater reduction of molecular burden had a 100% progression-free survival rate[7]. A similar finding was demonstrated in our study. The overall survival at 50 months was 100% for patients who had cytogenetic response whereas the overall survival was 60% for those without response. Previous therapy with IFN-α did not seem to influence the overall survival in our patients.

Imatinib-induced adverse effects are common but usually not severe. Common non-marrow related side effects were superficial oedema, nausea, vomiting, diarrhoea, muscle cramp and skin rash. Grade 3 or 4 hepatoxicity occurred in less than 5% of patients. Kantarjian *et al* reported skin rashes to be the most common among his patients. Six out of 261 patients (2%) had this adverse effect. Other side effects were less common and ranged from 0.4% to 2%[8]. Our patients had much higher non-marrow related adverse effects compared to Western studies. Fourteen percent developed peripheral oedema, 12% had gastrointestinal side effects (nausea, vomiting, and diarrhoea) and 7% of them had skin rashes. These observations may be related to the smaller sample size of our study and perhaps the different genetic makeup of the Asian population. However, the side effects were not severe enough to cause permanent interruption of treatment. We found that gastrointestinal side effects were significantly more common in patients taking 600mg or higher doses of imatinib. This could be explained by the relatively smaller body weight of our population.

Myelosuppression has also been frequently reported in clinical trials [3-7, 12]. It is more common in patients with advanced disease. There was no permanent discontinuation of treatment because of myelosuppression in our study. Forty five percent of our patients who were less than 60kg developed anaemia compared to only 14% in those weighing more than 60kg (p value < 0.0005). More patients who weighed less than 60kg developed thrombocytopenia and neutropenia but this was not statistically significant. Therefore, it is important for careful monitoring of peripheral blood count in smaller size patients to allow timely action in preventing more serious complications. It is impractical to reduce the dose of imatinib to minimize side effects as its efficacy may be compromised. Furthermore, the overall imatinib-induced myelosuppression in our local patients were not more common than heavier built Western patients.

In conclusion, our local CML patients did well on imatinib treatment. The response rate was as good as in Western studies. The factors affecting the response were phase of the disease and presenting white cell count. Adverse effects in our patients were mild and tolerable. Gastrointestinal side effects were commoner in patients taking 600mg or higher dose of imatinib. Anaemia developed more frequently in smaller sized patients. Anemia was also a negative predictor of cytogenetic response. Advanced disease, absence of cytogenetic response and high presenting white cell counts predicted poor prognosis.

Last but not the least, more efforts are needed to identify predictors of cytogenetic response as these can guide physicians when deciding between allogeneic haemopoietic stem cell transplantation and drug therapy as the optimal treatment for an individual. The patients should be involved in the decision making

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