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An update on imatinib mesylate therapy in chronic myeloid leukaemia patients in a teaching hospital in Malaysia

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INTRODUCTION The introduction of imatinib mesylate in 1998 has changed the management of chronic myeloid leukaemia. It is now the first-line therapy for newly diagnosed chronic myeloid leukaemia patients worldwide. However, its long-term survival benefit still needs to be established in clinical setting among Asian patients.

METHODS All chronic myeloid leukaemia patients in the chronic phase who were on imatinib mesylate therapy were retrospectively reviewed. Data was collected through a review of case notes, which was then processed, managed and analysed.

RESULTS A total of 44 patients were included in the study. The cumulative rates of complete haematological response, major cytogenetic response and major molecular response were 93.2%, 75.0% and 34.2%, respectively. The overall survival and event-free survival at five years were 86.0% and 84.9%, respectively. 31.8% of the patients developed anaemia, 29.5% neutropenia and 27.3% thrombocytopenia. A total of 43.2% of patients developed non-haematological side effects. Higher dosage (> 600 mg) and smaller body size (< 60 kg) were risk factors for haematological side effects. Patients with major cytogenetic response and absence of thrombocytopenia had better survival.

CONCLUSION The majority of our chronic myeloid leukaemia patients did well with imatinib therapy. The adverse effects in our patients were tolerable, and no patient had to stop treatment permanently.

Keywords: chronic myeloid leukaemia, chronic phase, imatinib mesylate, major cytogenetic response, overall survival
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INTRODUCTION

Chronic myeloid leukaemia (CML) is a malignant haematopoietic stem cell disorder, which accounts for 15% of patients with leukaemia.[1] It is characterised by the presence of Philadelphia chromosome, which is a balanced translocation between the long arms of chromosomes 9 and 22 [t (9; 22) (q34; q11.2)]. This translocation results in a *BCR-ABL* fusion gene, which translates into a chimeric BCR-ABL protein that has deregulated tyrosine kinase activity.[2] The haematopoietic stem cell that acquired this constitutively active tyrosine kinase has increased proliferative activities and reduced apoptosis, which give rise to the typical features of CML. About 90% of patients are diagnosed in the chronic phase of the disease but will progress to the accelerated phase, and finally, blast crisis, if left untreated within 3–5 years.[3,4] The prognosis for patients in the blast phase is poor, as they do not respond well to treatment.[5]

Imatinib mesylate (Novartis Oncology) is an agent that targets the constitutively active tyrosine kinase, which has revolutionised the treatment of CML over the last few years. Haematopoietic stem cell transplantation and α-interferon were the treatments of choice in newly diagnosed patients before the era of imatinib, as long-term survival and possibly, cure can only be achieved with these two modalities.[6,7] However, only a small number of patients responded to α-interferon; moreover, both the treatments are associated with considerable adverse effects. Currently, imatinib is the first line of treatment, with haematopoietic stem cell transplantation reserved for patients who demonstrate resistance to imatinib.[8]

Several studies have shown good response in CML patients treated with imatinib. These studies also showed an improved overall survival.[9-13] More recently, the five-year follow-up of the International Randomized Study of Interferon and ST1571 (IRIS) trial was presented. The event-free survival at five years was 83% and the rates of complete haematological response, major cytogenetic response and complete cytogenetic response (CCyR) were 97%, 88% and 82%, respectively.[14] Our previous data has shown that Asian patients did equally well, but the total follow-up duration was short.[15] Therefore, this follow-up study aimed to look at the long-term outcome and side effect profile of our patients.

METHODS

This was an observational study. All patients with CML in the chronic phase who were treated with imatinib were analysed. The patients' characteristics, responses to imatinib and adverse effects were examined. Their profile was reviewed until June 30, 2009.

Complete haematological response was defined as white blood cell count < 10×10^9/L, platelet count < 450×10^9/L, presence of < 5% myelocytes plus metamyelocytes, < 20% basophils and absence of blasts and promyelocytes in the

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peripheral blood, extramedullary involvement, as well as a blast value < 5% in the bone marrow lasting for more than four weeks.[16] Cytogenetic response was based on the prevalence of Ph-positive metaphases among at least 20 metaphases investigated in each bone marrow sample, and was defined as complete (0% Ph-chromosome-positive cells in metaphase), partial (1%–35% Ph-chromosome-positive cells in metaphase), minor (36%–65% Ph-chromosome-positive cells in metaphase), minimal (66%–95% Ph-chromosome-positive cells in metaphase) or none (> 95% Ph-chromosome-positive cells in metaphase). A major cytogenetic response included complete and partial cytogenetic responses (Ph 0%–35%).[16]

Molecular monitoring was done by measuring the number of BCR-ABL transcripts in the peripheral blood using reverse transcription-polymerase chain reaction (RT-PCR) method. Major molecular response is defined as BCR-ABL/ABL ratio ≤ 0.1%. Complete molecular response refers to no detectable BCR-ABL transcripts by RT-PCR at a sensitivity of 10^{-4}. A reduction of < 3-logs is said to be a minor molecular response.[16] Any of the following events were considered as disease progression: death from any cause during treatment; disease progressed into more advanced phases; and loss of complete haematologic and/or major cytogenetic responses.[9] Duration of response was calculated from the first reported date of response to the earliest date of reported relapse or death. Time to progression was defined as the time from the start of treatment to the onset of an accelerated or blastic phase, discontinuation of therapy due to unsatisfactory therapeutic effects, or death. Survival was calculated from the beginning of therapy until the time of death from any cause.

Haematological side effects, including neutropenia, thrombocytopenia and anaemia, were recorded. Neutropenia and thrombocytopenia in chronic-phase patients were defined as < 1 × 10^9/L and < 50 × 10^9/L, respectively. Neutropenia and thrombocytopenia in advanced disease were defined as < 0.5 × 10^9/L and 10 × 10^9/L, respectively. Anaemia was defined as haemoglobin (Hb) < 10 g/dL.[9] Data were processed, managed and analysed using the Statistical Package for the Social Sciences version 16.0 for Windows (SPSS Inc, Chicago, IL, USA) in order to determine the factors that significantly affect the response rate, survival and adverse effects. Frequencies and descriptive statistics were also generated using the same programme. Differences among variables were evaluated by the chi-square test. Survival probabilities were estimated by Kaplan-Meier's method. Results were considered statistically significant at $p < 0.05$.

RESULTS

A total of 44 patients participated in the study; 28 (63.6%) were male and 16 (36.4%) were female. The duration of disease was 12–232 (median 37) months and the duration of survival was 12–102 (median 35) months. The median age of the patients was 48 (range 15–73) years. Ten (22.8%) chronic phase patients had received interferon prior to receiving imatinib. The maintenance dose for the majority of patients was 400 mg (63.6%), followed by 600 mg (15.9%), 800 mg (9.1%) and 300 mg (9.1%). Table I shows the characteristics of the patients. Table II shows the various responses of the patients to treatment. The cumulative complete haematological response rate was 93.2%. Major cytogenetic response was achieved in 27 (75.0%) patients, out of which 23 (63.9%) of these were in complete response while the remaining four (11.1%) were in partial response. Six (15.8%) patients achieved major molecular response, while seven (18.4%) had complete molecular response.

Table I. Patient characteristics (n = 44).

Characteristic	No. (%)
Gender	
Male	28 (63.6)
Female	16 (36.4)
Ethnicity	
Malay	12 (27.3)
Chinese	26 (59.1)
Indian	6 (13.6)
Weight (kg)	
< 60	15 (34.1)
≥ 60	29 (65.9)
Imatinib maintenance dose (mg)*	
300	4 (9.1)
400	28 (63.6)
600	7 (15.9)
800	4 (9.1)

* One patient was still on 100 mg due to intolerance (severe neutropenia).

Table II. Overall responses of chronic phase patients to imatinib.

Response	No. (%)
Haematological (n = 44)	41 (93.2)
Cytogenetic (n = 36)*	
Major	27 (75.0)
Complete	23 (63.9)
Partial	4 (11.1)
Molecular (n = 38)†	
Complete	7 (18.4)
Major	6 (15.8)
Minor	11 (28.9)
No response	14 (44.7)

* Six patients were too early to monitor cytogenetic responses and cytogenetic study was not done in two patients,.
† Six patients were too early to monitor molecular responses.

The adverse effects of imatinib on our patients were mild to moderate. There was no permanent discontinuation of treatment as a result of these adverse effects. The rate of non-haematological side effects was 4.5%–43.2%, while that of haematological side effects was 27.3%–31.8% (Table III). Imatinib-induced thrombocytopenia was a negative predictor for cytogenetic response and survival. Patients who did not develop thrombocytopenia had better cytogenetic response (83.3% vs. 44.4%, $p = 0.025$).

In this analysis, the dose of imatinib and weight of patients were noted to influence the haematological side effects. Patients who were on ≥ 600 mg dosage had statistically higher rates of

Table III. Side effects of imatinib.

Side effect	No. (%)
Anaemia	14 (31.8)
Neutropenia	13 (29.5)
Thrombocytopenia	12 (27.3)
Oedema/weight gain	19 (43.2)
Liver toxicity	14 (31.8)
Musculoskeletal pain	13 (29.5)
Gastrointestinal side effects	10 (22.7)
Skin rashes	5 (11.4)
Headache, giddiness, tinnitus	6 (13.6)
Hypopigmented skin	2 (4.5)

Table IV. Factors affecting survival.

Factor	Survival (%)		p-value
	Yes	No	
Haematological response			< 0.001
Yes	100	0.0	
No	25.0	75.0	
Major cytogenetic response			< 0.001
Yes	84.4	15.6	
No	0.0	100	
Thrombocytopenia			0.025
Yes	75.0	25.0	
No	96.9	3.1	
Anaemia			0.052
Yes	78.6	11.4	
No	96.7	3.3	

neutropenia (p = 0.04). Patients who weighed < 60 kg had a higher risk of developing anaemia (53.3% vs. 20.7%), thrombocytopenia (53.3% vs. 13.8%) and gastrointestinal tract side effects (40.0% vs. 13.8%), which were also statistically significant, with p = 0.028, p = 0.005 and p = 0.049, respectively. However, for patients on a 400 mg dosage, thrombocytopenia was the only statistically significant haematological adverse effect if they weighed < 60 kg (37.5% vs. 5.0%, p = 0.026).

Survival was affected by cytogenetic response, haematological response and thrombocytopenia (Table IV). Patients who achieved haematological and cytogenetic responses had significantly higher survival rates than those who did not (p < 0.001). Kaplan-Meier analysis estimated that 80% of patients who achieved haematological response would survive, but none of those without haematological response would survive at eight years. On the other hand, the survival rate for those who achieved major cytogenetic response at eight years was 100%, but for those who did not, the survival rate was only 50% (Fig. 1). Patients with imatinib-induced thrombocytopenia were found to have significantly lower survival rates compared to those without thrombocytopenia (72.0% vs. 96.9%, p = 0.025) (Fig. 2). The overall survival in this cohort was 86.0% and event-free survival was 84.9% at five years. Four patients died; three of them were primarily refractory to imatinib and one achieved haematological response for a short period of time.

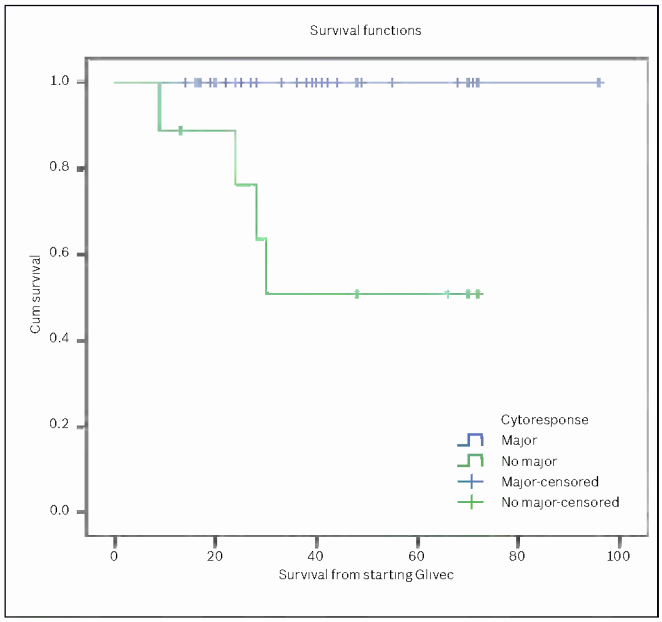

Fig. 1 Graph shows major cytogenetic response vs. survival (months).

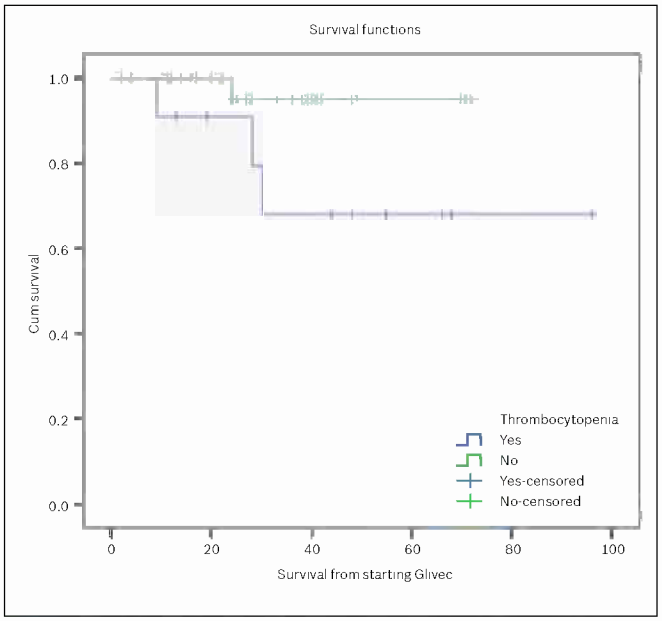

Fig. 2 Graph shows thrombocytopenia vs. survival (months).

DISCUSSION

The introduction of imatinib in 1998 changed the treatment algorithm of CML. It is now the first-line treatment for newly diagnosed CML patients worldwide. However, the long-term safety profile and survival benefit still need to be established, especially in the clinical setting, among Asian patients. Therefore, it is important to continue monitoring and updating the outcome in this group of patients. The updated IRIS trial showed that the cumulative incidence of CCyR was 87% at 60 months with five-year event-free survival and overall survival of 83% and 89%, respectively.[14] In comparison, our cohort had CCyR of 63.9%, five-year event free survival of 84.9% and overall survival of 86.0%. Our CCyR is comparable to other clinical data,[10-12] even though it is inferior to that of the IRIS trial. This is because some of our patients had previous treatments before receiving imatinib, but patients in the IRIS trial were all newly diagnosed CML patients.

The initial dose of imatinib (600 mg), Hb level (at least 10 g/dL), platelet count (at least 100 × 10^9/L) and peripheral blood blast level (below 50%) had been shown to be independent predictors for sustained complete haematological response.[17] In our study, we did not identify any factors that influence the haematological response. High platelet counts and > 90% Ph positivity prior to starting imatinib mesylate were identified as independent adverse prognostic factors for achieving complete cytogenetic response.[18] Other studies have found that imatinib-induced neutropenia was a negative predictor of cytogenetic response.[12,19] In our study, imatinib-induced thrombocytopenia was a predictor of poor cytogenetic response. Interruption of therapy is postulated as the culprit of poor response in patients with myelosuppression.[20] Imatinib-induced cytopenia had shown contradictory results for the impact on event-free survival.[22,23] Our study also revealed that imatinib-induced thrombocytopenia was an indicator of poor survival. Only 72% of imatinib-induced thrombocytopenia patients were found to have survived at eight years compared to 96.9% of patients who did not develop thrombocytopenia. Imatinib-induced neutropenia or anaemia did not influence the survival of our patients.

In addition, haematological resistance to α-interferon, splenomegaly and the lack of any cytogenetic and molecular responses were shown to be independent poor prognosticators in various reports.[18,21,24] In contrast, we found that previous therapy with α-interferon and splenomegaly did not confer a poor prognosis for our patients, whereas a lack of haematological and cytogenetic responses as well as imatinib-induced thrombocytopenia were poor prognostic factors. The overall survival at eight years was 100% for patients with major cytogenetic response and 50% for those without major cytogenetic response.

Imatinib-induced adverse effects are common but usually not severe. Common non-haematological side effects are superficial oedema, nausea, vomiting, diarrhoea, muscle cramp and skin rash. Kantarjian et al[21] reported skin rashes to be the most common side effect among their patients, and six out of 261 (2%) of their patients had this adverse effect. Other side effects cited (0.4%–2.0%) were less common.[21] On the contrary, our patients had much higher non-haematological adverse effects compared to patients in Western studies. 43.2% of our patients developed peripheral oedema, 29.5% had musculoskeletal complaints (joint pain, bone pain, myalgia and muscle cramps), 31.8% had liver toxicity, 22.7% had gastrointestinal side effects (nausea, vomiting, abdominal pain and diarrhoea) and 11.4% had skin rashes. These observations may be related to the smaller body size of our patients and probably the different genetic makeup of the Asian population. Nevertheless, these non-haematological side effects were tolerable and did not result in permanent interruption of treatment.

Myelosuppression has also been frequently reported in clinical trials.[17,18,25,26] Nearly one-third of our patients developed myelosuppression at the early phase of treatment. Smaller body size and a higher dose of imatinib were contributors to myelosuppression. Imatinib dosage ≥ 600 mg was a risk factor for developing neutropenia. On the other hand, patients weighing < 60 kg had a higher risk of developing anaemia and thrombocytopenia than those who weighed more (53.3% vs. 20.7% and 53.3% vs.13.8%, respectively). Kanda et al found that smaller size and older patients had poorer cytogenetic response, and treatment had to be interrupted in 45% of their patients due to myelosuppression (a cohort with median weight of 62.2 kg).[20] Kawaguchi et al concluded that a smaller dose of imatinib may be sufficient for the treatment of CML among patients with a smaller body size since they were able to achieve adequate trough imatinib levels when forced to take a reduced dose of 300 mg/day due to intolerability.[27] Therefore, close monitoring of smaller body size patients is important, especially at the initial stage of imatinib treatment, so that titration of the dose can be taken to prevent adverse effects from myelosuppression without compromising the efficacy of treatment.

In conclusion, the long-term outcome and responses of our patients are comparable to those of other studies. Even though the patients in our study suffered more side effects, especially smaller size patients, the treatment was still tolerable. However, myelosuppression together with advanced disease confer poorer response and prognosis. In addition, up to 30% of chronic phase patients may not have optimal response to imatinib. Therefore, the challenge in managing CML patients is to carefully identify and monitor high-risk patients so that alternative options, such as allogeneic haematopoietic stem cell transplantation and a new generation of tyrosine kinase inhibitors, could be offered before the progression of the disease, since the prognosis is extremely poor for advanced phase disease.

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