ABSTRACT

Objective: Data on the use of Imatinib (IM) in developing countries remain limited. A retrospective study was done to assess the efficacy and toxicity of IM in treating chronic myeloid leukaemia (CML) in Trinidad and Tobago.

Methods: Patients in all phases of CML who started IM therapy between February 2001 and February 2004 were included. All had received other previous therapy. They were assessed for haematological, cytogenetic and molecular response, overall survival (OS), event free survival (EFS) and adverse effects (AE).

Results: Twenty-five patients were followed-up for a median 61 months. At initiation of IM, 18 were in the chronic phase (CP), 3 in accelerated phase (AP), 3 in blast crisis (BC) and one in myelofibrotic transformation (MF). Overall, 96% of patients achieved complete haematological remission (CHR). Among CP patients, 67% attained a major cytogenetic response (MCR) and 44% a complete cytogenetic response (CCR). Overall survival and event free survival in the CP group were 82% and 76% respectively. Overall survival for advanced phase patients was 14% at 61 months. The adverse effects of IM were the same as previously described and generally tolerable. No patient opted to discontinue IM because of side effects.

Conclusion: After 5 years of follow-up, IM was found to induce favourable and durable survival responses with an acceptable side effect profile in CP-CML patients who had received prior treatment with alternative agents.

Keywords: Chronic myeloid leukaemia, efficacy, toxicity, imatinib
INTRODUCTION
Chronic Myeloid Leukaemia (CML) is a stem cell malignancy defined by the presence of the Philadelphia Chromosome and/or its molecular counterpart, the bcr – abl fusion gene. A constitutively active tyrosine kinase causes uncontrolled myeloid proliferation and three phases of disease: the chronic phase (CP) which typically lasts 3–5 years, a variable accelerated phase (AP) with median survival 1–2 years and the blast crisis (BC), myeloid or lymphoid, with survival measurable in months (1). Most patients present in the CP with leucocytosis and splenomegaly and progress to the advanced phases of AP or BC. A few undergo transformation to myelofibrosis (MF).

Hydroxyurea therapy controls the disease in the CP for 35–65 months without eliminating the Philadelphia chromosome or preventing progression. Interferon (IFN) induces Philadelphia chromosome negativity and prolongs survival but can cause fevers, chills, flu-like symptoms, depression and fatigue, affecting quality of life and compliance. Interferon therapy is discontinued in 15–25% of persons with CML because of intolerable side effects. The addition of cytosine arabinoside to IFN improves the cytogenetic response but has not been shown to increase survival further. Stem cell transplantation from an HLA-matched sibling is potentially curative but carries an estimated 15–25% procedure related mortality.

Imatinib mesylate (IM) is a relatively specific bcr-abl tyrosine kinase inhibitor with proven superiority over IFN and cytosine arabinoside in all phases of CML (2). Tyrosine kinase inhibition results in highly efficient elimination of the Philadelphia chromosome or bcr-abl containing clone in haemopoietic tissue. Many of its common side effects are mediated by inhibition of tyrosine kinases in other tissues (3). There remains a paucity of data on the efficacy and safety of IM from the developing world (4–6).

SUBJECTS AND METHODS
A retrospective study of all CML patients who started IM therapy between February 1, 2001 and January 31, 2004 at the Port-of-Spain General Hospital, Trinidad, was conducted. The cut-off date for this analysis was February 1, 2009. Patients were categorized by age, ethnicity, leucocyte count and splenic size at presentation, disease phase at start of IM, preceding therapy, delay before IM therapy, best cytogenetic response, overall survival (OS), event free survival (EFS) and adverse effects (AE).

Philadelphia chromosome testing was done by the G-banding technique, examining a minimum of 20 metaphases. Bcr-abl was detected by real time polymerase chain reaction (RT-PCR) or Fluorescent in situ Hybridization (FISH). Standard criteria were used to assign disease phase (1). An Imatinib dose of 400 mg daily was used to treat the chronic and 600 mg daily the advanced phases. Cytogenetic testing was performed at least once per year.

Complete haematological response (CHR) was defined as normalization of complete blood count and blood film with disappearance of clinical signs and symptoms. Response was additionally categorized by the best cytogenetic response: complete (CCR), if no Ph-positive cells were present, partial (PCR), if the proportion of Ph-positive cells was between 1 and 34% and minor (minor CR) if the proportion of Ph-positive cells declined to between 35 and 90%. Major cytogenetic response (MCR) was defined as the sum of partial and complete responses. No response (NR) was defined as Ph-positive cells above 90%. Signs of a complete molecular response (CMR – no bcr-abl transcripts detected) were sought if CCR was obtained. Survival was measured from the time of starting IM to death from any cause. Event free survival was defined by the first occurrence of any of the following: death from any cause, progression from CP to AP or BC or loss of a cytogenetic response (> 30% increase in Ph-positive cells). Statistical analysis was performed with
SPSS version 12 for Windows. Survival between the two phases (chronic versus advanced) was examined by the Kaplan-Meier estimator. Survival analysis using all patients and statistical significance were determined by the log rank test.

RESULTS

Twenty-five CML patients started IM during the study period and were followed-up for a median 61 months. Thirteen were males and 12 females, giving a male:female ratio of 1:1. Eleven (44%) were of Indian descent, 8 (32%) mixed, 5 (20%) African and one (4%) Chinese. Ages ranged from 16 to 73 (median 44) years.

Median leucocyte count at diagnosis was 123 (range 34 – 368) x 10⁹/l and 23 (92%) had clinical splenomegaly extending 2 – 26 (median 5) cm beneath the left costal margin. Preceding therapy was with hydroxyurea (HU) only in 17 (68%) cases, hydroxyurea then interferon (IFN) in 6 (24%) and hydroxyurea then cytosine arabinoside/interferon in 2 (8%). The median time between initial diagnosis of CML and IM therapy was 15 (range 2 – 85) months.

At initiation of IM therapy, 18 patients were in chronic phase (CP) and 7 in advanced phases – 3 accelerated phase (AP), 1 myelofibrotic (MF) transformation and 3 in blast crisis (BC), 2 myeloid and 1 lymphoid. Overall, 96% achieved complete haematological remission (CHR). Three patients in BC at the start of IM succumbed to their disease within 6 (median 4.3) months. One of three patients in AP with an additional abnormality of chromosome 1q reverted to 100% Ph with disappearance of the 1q abnormality and remained alive in CHR 64 months after starting IM. The other two AP patients progressed to acute myeloblastic leukaemia and died within seven months of starting IM.

Among CP patients, there were 12 (67%) MCR including 8 (44%) CCR and 4 (23%) PCR. Minor CR and NR accounted for 22% and 11% respectively (Fig. 1). All patients achieving CCR also attained CMR. There were 3 deaths in CP patients, one each from ischaemic heart disease, bronchogenic carcinoma and progression to acute myeloblastic leukaemia. One admittedly non-compliant patient had a minor CR and there were 2 (11%) cases of genuine NR despite escalation of IM dose. They remained alive in CHR at 61 and 64 months respectively at the end of the study. Estimated OS and EFS were 83% and 77% at 61 months for CP. Estimated survival at 61 months for patients achieving CCR was 100%. Overall survival for all patients was 60% at five years.

The most common side effect of IM was skin hypopigmentation (65%) followed by cramps (45%) and weight gain (20%). Grade IV myelosuppression, flatulence, pleural effusion and Stevens-Johnson syndrome each accounted for 5%. There was one case of autoimmune haemolytic anaemia in an AP patient after 59 months of IM. This was successfully managed by temporary IM discontinuation and immunosuppressive steroid therapy. No patient opted to discontinue treatment due to intolerable severe side effects.

Age, gender and ethnicity showed no univariate relationship with survival (p > 0.05 in all cases). Fig. 2 shows that patients in the chronic phase had a longer survival after initiation of treatment compared to those in the APs (median survival 65 versus 11 months, p = 0.001). The Cox’s proportional hazards model with age and delay between diagnosis and initiation of IM as covariates, also showed that patients in the CP were more likely to survive (p = 0.028). Using this model, it was found that delay in initiation of treatment was inversely related to survival (regression coefficient = -0.096, p = 0.048).
DISCUSSION
Trinidad and Tobago is a developing country in which only 4.2% of the gross domestic product (GDP) is spent on health. Gross domestic product per capita in 2007 was $17 403 US (7). The annual incidence of CML is approximately 1 per 100 000 population. Cytogenetic or molecular analysis is not locally available and specimens are shipped abroad for testing. Stem cell transplantation is not done on the island but could be undertaken at the patient’s expense in a developed country, usually the United States of America (USA), Canada or England. Imatinib is provided in government hospitals at no cost to the patient. Whereas, therefore, locally performed stem cell transplantation was found to be cost effective compared to IM in Mexico (8), IM is the practical first option in Trinidad and Tobago.

Imatinib was first used in Trinidad and Tobago in 2001 to treat patients who had transformed to advanced phases of CML. Following FDA approval for the indication in 2003, all newly diagnosed CML patients were treated with IM after cytogenetic confirmation and induction of CHR with hydroxyurea.

Among the advanced disease patients treated in 2001, the patient with MF transformation and one with acutely newly diagnosed CML patients were treated with IM after hydroxyurea.

Among the advanced disease patients treated in 2001, the patient with MF transformation and one with acute lymphoblastic transformation had fully HLA-matched siblings but no access to stem cell transplantation. The patient in lymphoid BC attained CHR on IM, subsequently underwent identical twin allogeneic SCT in England but relapsed and died within three months of IM. The myelofibrotic patient succumbed to complications of bone marrow failure 10 months after starting IM.

The majority of adverse effects were mediated by inhibition of other tissue tyrosine kinases. Hypopigmentation, the most common side effect in the present study, is possibly mediated by inhibition of the melanocyte c-Kit receptor tyrosine kinase. Flatulence and diarrhoea are probably related to C-Kit inhibition in the interstitial cells of Cajal which have a pacemaker function in the intestine. The mechanisms of cramps, weight gain and fluid retention remain unknown. Grade IV myelosuppression necessitated red cell and platelet transfusions in one patient. Autoimmune haemolytic anaemia due to IM in one patient was accompanied by severe anaemia (haemoglobin 3.6 g/dL) and strongly positive direct antiglobulin test with spherocytes and polychromasia on blood film (Fig. 3). To the best of the authors’ knowledge, this has been reported only once in the literature (9).

Despite the size of the study sample and the constraints which prevented more frequent cytogenetic testing, the results indicate responses to IM in CP patients that are comparable to pre-treated patients in the developed world (10) and superior to Jamaican CML patients in the pre-Imatinib era (11). They could improve further if the delay between diagnosis and initiation of IM is reduced by introducing cytogenetic and molecular analysis locally. Side effects were the same as previously described and tolerable.

The poor results in patients with advanced disease support the NICE recommendation that IM be considered only as an option in this setting (12). Despite the poor survival of patients with advanced disease, IM was found to be useful for palliation without the toxicity of induction chemotherapy.

In summary, this analysis provides evidence of similar efficacy and safety of IM to treat CML in Trinidad and Tobago to that demonstrated in the developed world. Toxicity is mild and side effects are the same as previously described. Further analysis is needed to compare responses to IM in the different ethnic groups in Trinidad and Tobago.

REFERENCES