Clinical Characteristics and Hematologic Responses to Imatinib in Patients with Chronic Phase Myeloid Leukemia (CML) at Cipto Mangunkusumo Hospital


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ABSTRACT

Aim: to analyze the clinical characteristics of patients with chronic phase CML and evaluate complete hematologic responses (CHR) and overall survival (OS) after treatment with Imatinib.

Methods: this is a cross sectional study using retrospective medical record of patients with chromosome Philadelphia positive and/or BCR-ABL positive chronic phase CML at the polyclinic of Teratai Department of Internal Medicine Cipto Mangunkusumo National Hospital during 2003-2008.

In a period of 6 years, we included 53 patients with chromosome Philadelphia positive and/or BCR-ABL positive chronic phase CML. Patients were administered Imatinib 400 mg daily and then evaluation of clinical characteristics and complete blood count + differential count were performed every 2 weeks until CHR achieved at 3 months as defined by white cells count <10.000/mm³, platelet count <450.000/mm³, and non palpable spleen.

Results: the median age was 37 years (16-67 years). Males were slightly more frequent than females (29 v.s. 24) with ratio of 1.2:1. Thirty three percent of patients had splenomegaly. The vast majority (60%) of patients had previous treatment with Hydroxyurea. The laboratory features were: median of hemoglobin level was 10.0 g/dL (6.3-16.6 g/dL), median of white-cell count was 13.300/uL (6.2-400.000/uL), and median of platelet count was 424.000/uL (108.000-4.400.000/uL). Median of basophils was 1.6% (0%-20%) and 88% of patients had <5% blasts in bone marrow.

Conclusion: A CHR was achieved in 74% of patients and overall survival during the study was 66%. The most common adverse events were: nausea, myalgia, hypopigmentation of the skin, anemia, thrombocytopenia, and neutropenia.

Key words: clinical characteristic of patients with chronic phase CML, Imatinib, hematologic response.

INTRODUCTION

Chronic myeloid leukemia (CML) is a chronic hematologic malignancy characterized by the presence of the Philadelphia chromosome (Ph), a consequence of an aberrant reciprocal translocation of genetic material between chromosome 9 and 22, resulting in the fusion of portions of the genes encoding BCR and ABL. The BCR-ABL fusion gene encodes a constitutively active leukemogenic protein-tyrosine kinase which results in continuous cell growth and replication. Imatinib mesylate is a small molecule signal transduction inhibitor that specifically targets a limited set of protein tyrosine kinase and their oncogenic form, most notably BCR-ABL. Imatinib mesylate, a targeted inhibitor of BCR-ABL tyrosine kinase, is the standard of care for chronic myeloid leukemia. A phase 2 trial of Imatinib in late chronic-phase (CP) CML after interferon (IFN) failure reported that complete hematologic response (CHR) and overall survival (OS) were 96% of patients at some point during the study and 76%, respectively. We aim to analyse the clinical characteristic of patients with chronic phase CML and evaluate CHR and OS after treatment with Imatinib.

METHODS

This is a cross-sectional study that investigated the clinical characteristics and outcome of Imatinib therapy in patients with chromosome Philadelphia positive and/or BCR-ABL positive chronic phase (CP) chronic myeloid leukemia (CML) at the Polyclinic of Teratai Cipto Mangunkusumo National Hospital (RSCM) during 2003-2008. Analysis of Philadelphia chromosome was performed by cytogenetic karyotype. The measurement of BCR-ABL transcript levels is
evaluated by reverse transcriptase polymerase chain reaction (RT-PCR) multiplex. The method used set primer CA3-, C5e-, B2B, and BCR-C which can detect mRNA fusion gene BCR-ABL transcript exon e13a2, e14a2, e1a2, and normal BCR gene as internal control. Chronic Phase CML was defined by the presence of less than 15% blasts and less than 30% blasts plus promyelocytes in the peripheral blood and bone marrow, less than 20% peripheral basophils, and a platelet count of at least 100,000/mm³. The primary objective was the clinical characteristic of patients with chronic phase CML and secondary objectives were complete hematologic responses (CHR), overall survival (OS), and adverse events of Imatinib. Patients were administered Imatinib 400 mg daily and then evaluation of clinical characteristic and complete blood count + differential count were performed every 2 weeks until CHR achieved at 3 months as defined by white cells count <10,000/mm³, platelet count <450,000/mm³, and non palpable spleen. Overall survival was censored from the first time consuming Imatinib until the last contact date for patients still alive. We made a note of any adverse events of Imatinib from the medical record on every patient visit to the polyclinic based on WHO recommended toxicity gradings.

RESULTS

Clinical and Laboratory Characteristic of Patients with Chronic Phase CML

A total of 53 patients with chromosome Philadelphia positive and/or BCR-ABL positive chronic phase CML were evaluated during 2003-2008. The median age was 37 years (16-67 years) with only 7% of patients were >=60 years. Males were slightly more frequent than females (29 vs 24) with ratio of men and women was 1.2 : 1. Thirty three percent of patients had splenomegaly. The laboratory features of patients with chronic phase CML: median of hemoglobin (Hb) level was 10.0 g/dL (6.3-16.6 g/dL) with 74% of patients had a Hb level <12 g/dL, median of white-cell count was 13.300/uL (1900-621.000/uL), and median of platelet count was 424.000/uL (108.000-4.400.000/uL). Median of basophils was 1.6% (0%-20%) and 88% of patients had <5% blasts in bone marrow.

Efficacy

A CHR (Complete Hematologic Responses) was achieved in 74% of patients at 3 months during the study. The Overall Survival during the study was 66%.
**Safety**

Common non-hematologic adverse events included nausea (60%), myalgia (53%), and hypopigmentation of skin (47%). Common hematologic adverse events included mild anemia (20%), mild thrombocytopenia (14%), and mild neutropenia (4%). Both of the adverse events were grade 1 based on WHO recommended toxicity gradings.

**DISCUSSION**

Chronic myeloid leukemia (CML), also called chronic granulocytic leukemia, is a clonal myeloproliferative disorder of hematopoietic stem cells that is characterized by overproduction of cells of the myeloid series, which results in marked splenomegaly and leukocytosis. Basophilia and thrombocytosis are common. Most patients (85% to 95%) were in the chronic phase. Eventually, if poorly controlled, CML evolves into the accelerated and blastic phases. A total of 53 patients with chromosome Philadelphia positive and/or BCR-ABL positive chronic phase CML were evaluated during 2003-2008 at the Polyclinic of Teratai Department of Internal Medicine Cipto Mangunkusumo National Hospital (RSCM). The median age of patients was 37 years (16-67 years) with only 7% of patients were ≥60 years. At MD ANDERSON Cancer Centre, the median age of patients with chronic phase CML at diagnosis is 45-55 years with 26% of patients are ≥60 years; even NCCN stated that the median age of disease onset is 67 years eventhough CML occurs in all age groups.5 The median age of patients with chronic phase CML at RSCM is younger and less patients are ≥60 years compared to MD ANDERSON Cancer Center and NCCN. Younger patients may result from unknown genetic variations, and needs further research since it has implications in terms of both the requirement for long terms imatinib therapy and for female patients of childbearing age since the side effect of imatinib to pregnant women that they have to consider participating in the family planning program.

Patients with chronic phase CML at RSCM were slightly more frequent in male (29 of 53) than female (24 of 53) with male to female ratio 1.2 : 1. This is not different from literature which reported that CML occurs slightly more frequently in men than in women with an incidence of ratio of 1.4-2.2:1.6,7 Thirty three percent of patients had splenomegaly. Splenomegaly, the most consistent physical sign of CML, occurs in 50%-60% of cases.4 The proportion of splenomegaly at RSCM is lower due to majority of patients had history of treatment with Hydroxyurea before Imatinib treatment so that the enlargement of spleen is smaller or even disappeared than at the first onset of the disease.

**Laboratory Features of Patients with Chronic Phase CML**

Kantarjian et al reported that in patients with late-chronic phase CML in whom previous therapy with interferon alfa had failed, median of Hb level was 12.5 g/dL (7.3-17.2) with only 38% of patients with chronic phase CML who had Hb level <12 g/dL.8 Diagnosis of CML is usually suspected in a patient with increased white blood cell count. The number of circulating mature and immature granulocytes can be markedly increased. Counts of 50,000 to 200,000/mm³ or higher are common with a median of 150,000/mm³. The majority of these cells are mature granulocytes, although metamyelocytes, myelocytes, promyelocytes, and even few blasts may be observed. Blasts are usually less than 5%. Basophilia and eosinophilia of granulocytes may be present. The platelet count may be normal or elevated (sometimes to strikingly high levels).10,11 Median of white-cell count patients with chronic phase CML at RSCM is lower due to history of treatment with Hydroxyurea so that the white-cell count decreased. Kantarjian et al reported that in patients with late-chronic phase CML in whom previous therapy with interferon alfa had failed, the median white-cell count was 15.000/mm³ (2.000-260.000/mm³).8 Median of basophil cell count is lower also due to history of treatment with Hydroxyurea. The vast majority of subjects with CP CML were administered hydroxyurea as previous treatment. Hydroxyurea, a ribonucleotide reductase inhibitor, is a well-tolerated oral cytotoxic agent that can control blood counts rapidly in most patients with CML. Hydroxyurea is the mainstay of treatment of CP CML patients in Indonesia. Hydroxyurea may be used for initial cytoreduction, as a temporary measure to control counts in between definitive therapies, or part of a combination approach with imatinib. It should not be used alone as a definitive treatment in CML, because it rarely suppresses Ph+ cells.12 The discovery of the Ph chromosome and, subsequently, the identification of BCR-ABL have revolutionized treatment of CML. For the majority of pts with CML in CP, the standard of care is to maintain the pts in CP with Imatinib therapy.2,5,12 Management strategies of patients with chronic phase CML have been revolutionized by the BCR-ABL selective kinase inhibitor.12 Imatinib is a novel antineoplastic agent that specifically inhibits the BCR-ABL tyrosine kinase. Imatinib has a well-characterized and clinically measurable mechanistic basis for its activity.13 Hematologic response to Imatinib must be
evaluated every 2 weeks before complete hematologic response as defined by white cells count <10,000/mm³, differential without immature granulocytes and with less than 5% basophils, platelet count <450,000/mm³, and non palpable spleen. A CHR (complete hematologic responses) was achieved in 74% of our patients at 3 months during the study. Kantarjian and Cortes reported that in patients with chronic phase CML after interferon failure, the proportion of CHR is 60%-80%. The overall survival of our patients with chronic phase CML during the study (2003-2008) was 66%. Kantarjian and Cortes reported that in patients with chronic phase CML after interferon failure, the estimated survival at 5 year is 79%. The lower Overall Survival needs further evaluation and it maybe related to the younger age group of our patients.

The most common non hematologic adverse events of Imatinib to patients with chronic phase CML at our polyclinic were nausea (60%), myalgia (53%), and hypopigmentation of skin (47%). The most common hematologic adverse events of Imatinib to patients with chronic phase CML at our polyclinic were anemia (20%), thrombocytopenia (14%), and neutropenia (4%) and none of patients stopped the treatment because of adverse events. Druker et al reported that after a median follow-up of 6 months, the most commonly reported adverse events were edema (including peripheral and periorbital edema) (60%), muscle cramps (49%), diarrhea (45%), nausea (50%), musculoskeletal pain (47%), rash and other skin problems (40%), abdominal pain (37%), fatigue (39%), joint pain (31%), and headache (37%). Grade 3 or 4 adverse events consisted of neutropenia (17%), thrombocytopenia (9%), anemia (4%), elevated liver enzymes (5%), and other drug-related adverse events (17%).

CONCLUSION

The clinical characteristic of patients with chronic phase CML was: median age was 37 years (16-67 years), males were slightly more frequent than females with a ratio 1.2 : 1, 33% of patients had splenomegaly, and 60% of patients had previous treatment with Hydroxyurea.

A CHR (complete hematologic responses) was achieved in 74% of patients with chronic phase CML within 3 months during the study. Among our patients with chronic phase CML in whom 60% had previous treatment with Hydroxyurea, the overall survival during the study was 66%.

The most common adverse events of Imatinib to patients with chronic phase CML were: nausea, myalgia, hypopigmentation of the skin, anemia, thrombocytopenia, and neutropenia.

REFERENCES