Treatment of Chronic Myeloid Leukemia in Chronic Phase with Imatinib

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Abstract:

Objective: Imatinib (Gleevec®) is accepted to be the first line therapy for chronic myeloid leukemia-chronic phase (CML-CP) with positive Philadelphia chromosome (Ph'). This study is aimed to describe the complete hematologic response (CHR) among the patients with CML-CP with positive Ph' chromosome that are treated with imatinib 100-400 mg/day **Patients and Methods:** The CML-CP patients with positive Ph' who were treated with imatinib 100-400 mg/day at Maharat Nakohn Ratchasima Hospital during the year 2009-2013, were retrospectively reviewed. The CHR and side effects were evaluated at the third, sixth and twelfth months of treatment. Results: In 5-year duration, 43 patients, 28 males and 15 females, were treated with imatinib of 100-400 mg/day. Ages ranged from 3 to 77 years. At the 3rd, 6th and 12th months of treatment, the CHRs were 97.7%, 95.3% and 83.7%, respectively. The side effects included neutropenia, seven cases with grade 1, three with grade 2 and two cases with minimal nausea. There were five cases emerging blast crisis and three cases dying of various causes unrelated to therapy. **Conclusion:** Forty-three CML-CP patients are treated with imatinib of 100-400 mg/day. In one year, CHR is 83.7%. The side effect is neutropenia, 7 cases with grade 1, 3 with grade 2. Five cases develop blast crisis and three cases die of various causes unrelated to therapy.

Keyword: Imatinib, Chronic myeloid leukemia, Philadelphia chromosome, Complete hematologic response

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บทคัดย่อ: การรักษามะเร็งเม็ดเลือดขาวเรื้อรังในระยะเรื้อรังด้วย imatinib

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วัตถุประสงค์: Imatinib (Gleevec®) ได้รับการยอมรับให้เป็นยาขนานแรกในการรักษาผู้ป่วยมะเร็งเม็ดเลือดขาวเรื้อรังที่มี Philadelphia chromosome (Ph') และอยู่ในระยะเรื้อรัง (chronic myeloid leukemia-chronic phase หรือ CML-CP) วัตถุประสงค์ของการศึกษานี้ คือ ศึกษาการตอบสนองอย่างสมบูรณ์ทางโลหิตของผู้ป่วย CML-CP ที่มี Ph' chromosome ที่ได้รับการรักษาด้วย imatinib 100-400 mg ต่อวัน **ผู้ป่วยและวิธีการ:** ศึกษาแบบย้อนหลังผู้ป่วย CML-CP ที่มี Ph' chromosome ระหว่าง พ.ศ. 2552-2556 ที่ได้รับการรักษาด้วย imatinib 100-400 mg ต่อวัน ณ โรงพยาบาลมหาราชนครราชสีมาโดยดูการตอบสนองอย่างสมบูรณ์ทางโลหิตและ อาการไม่พึงประสงค์ ในเดือนที่ 3, 6 และ 12 **ผลการศึกษา:** ในระยะ 5 ปี มีผู้ป่วย 43 ราย ชาย 28 และ หญิง 15 รายรักษาด้วย imatinib 100-400 mg ต่อวัน ผู้ป่วยอายุระหว่าง 3 ถึง 77 ปีเมื่อครบ 3, 6 และ 12 เดือนผู้ป่วยมีอัตราการตอบสนองอย่างสมบูรณ์ทางโลหิต เป็นร้อยละ 97.7, 95.3 และ 83.7 ตามลำดับผลข้างเคียงมีเพียง neutropenia โดย 7 รายเป็นเกรด 1 และ 3 รายเป็นเกรด 2 อีก 2 ราย มีอาการคลื่นไส้เล็กน้อยมีผู้ป่วย 5 ราย ที่มี blast crisis และ 3 ราย ที่เสียชีวิตจากสาเหตุที่แตกต่างกัน และไม่เกี่ยวข้องกับการรักษา **สรุป:** ผู้ป่วย CML-CP 43 รายที่รักษาด้วย imatinib 100-400 mg ต่อวัน ครบ 1 ปี มีการตอบสนองอย่างสมบูรณ์ทางโลหิต ร้อยละ 83.7 ผลข้างเคียงได้แก่ neutropenia เกรด 1 มี 7 ราย เกรด 2 มี 3 ราย มี blast crisis 5 ราย มี 3 รายเสียชีวิตด้วยสาเหตุต่าง ๆ กันที่ไม่เกี่ยวกับการรักษา

คำสำคัญ: Imatinib, มะเร็งเม็ดเลือดขาวเรื้อรัง, Philadelphia chromosome, การตอบสนองอย่างสมบูรณ์ทางโลหิต

Introduction

Chronic myeloid leukemia (CML) is one of the myeloproliferative neoplasia (PMN), the autonomous proliferation of the hematopoietic stem cells as the clonal disease. Its hallmark of diagnosis is marked leukocytosis with basophilia and with increased all stages of myeloid maturation: segmented form, band form, metamyelo-cyte, myelocyte, promyelocyte and few or occasional myeloblast and must be confirmed by cytogenetics showing t(9; 22)(q3.4;q1.1)[1], and by reverse tran-scriptase polymerase chain reaction (RT-PCR) showing BCR-ABL transcripts in most cases[2].

The product of the BCR-ABL transcripts is the tyrosine kinase and it leads to a breakthrough drug, the tyrosine kinase inhibitor (TKI). When the patients with CML, chronic phase (CML-CP) are treated with imatinib, the first TKI in large clinical trials, it introduces the new terms: cytogenetic response and major molecular response into the clinical practice in oncology field. It can dramatically prolong the survival of most, but not all, patients with CML-CP. A median survival of CML patients treated with old generation oral chemotherapy, used to be 5 years, is transformed into one for which the survival in many

cases promise to be comparable to that of normal persons of similar age[3].

This study is aimed to study the patients with CML-CP who carry BCR-ABL and are treated with oral imatinib (Gleevec® by Novartis) as the first line therapy.

Patients and Methods

This retrospective study recruited the patients who were diagnosed as CML-CP in the year 2009-2013 in the departments of medicine and pediatrics, Maharat Nakhon Ratchasima Hospital. The diagnosis depended on the combination of marked leukocytosis with increased all stages of granulocytic series and markedly increased cellularity, particularly granulocytic series with normal maturation in the bone marrow. The peripheral blast must be less than 15%, basophilia < 20%, blast plus promyelocyte < 30% in the bone marrow[4] and all were proved to carry BCR-ABL translocation using RT-PCR test. At first, majority of the patients were primarily treated with hydroxyurea for two or three weeks during waiting for the process of registration of the Gleevec® International Patient Assistance Program (GIPAP) and then the treatment would be switched to imatinib mesy-late (Gleevec®) 100-400 mg a day, depending on the body weight.

All cases would be clinically and hematologically followed every month for the first three months and then every two or three months. When the absolute neutrophil counts (ANC) were less than 2,000/mm^3, the dosage of imatinib would be decreased. At the end of the third, sixth and twelfth months, the patients would be hematologically evaluated. If the total WBC fell within the normal range (4,000-10,000/mm^3), normal ANC without blast, they would be considered achieving the complete hematologic response (CHR).

The side effects of imatinib were generally and hematologically collected. The neutropenia was defined as follows: grade 1 $\geq$ 1,500-2,000, grade 2 $\geq$ 1,000-1,500, grade 3 $\geq$ 500-1000, grade 4 < 500/cu.mm[5].

Results

There were 43 patients, consisting of 28 males and 15 females, and 40 cases were treated under the support of the GIPAP. The ages ranged from 3 to 77 years, median 45 years. At the first presentation, the complete blood count was shown in the following table.

The first CBC data of 43 patients with CML-CP

	Mean $\pm$ SD
Hb concentration (g%)	9.6$\pm$1.8
Hct (%)	28.7$\pm$5.2
WBC (/mm^3)	170,084$\pm$81,688.3
Blast (%)	4.4$\pm$3.2 (N=22)
Promyelocyte (%)	6.2$\pm$5.1 (N=23)
Neutrophil (%)	54.7$\pm$14.4
Lymphocyte (%)	5.9$\pm$4.7
Basophil (%)	3.2$\pm$3.2 (n=30)
Platelet (/mm^3)	769,000.0$\pm$625,782.9

Of 43 patients, the anemia (Hb< 13 g% in males and < 12 g% in females) was found in 27 from 28 males (96.4%) and in 14 from 15 females (93.3%). Twenty-one patients (48.8%) had no peripheral blast whereas 20 patients (46.5%) had no promyelocyte. The peripheral blast ranged from 0 to 10, mean 4.4$\pm$3.2%

(N=22) and promyelocyte ranged from 0 to 20, mean 6.2±5.1% (N=23). Only 30 cases (69.8 %) had blood basophil, it ranged from 0 to 14%, mean 3.2±3.2%, median 2% (N=30).

At the end of the 3rd month of treatment with imatinib, CHR was achieved in 42 of 43 cases (97.7%), the side effects were neutropenia, three cases with grade 1, one case with grade 2, and minimal nausea with no need of specific treatment in two cases.

At the end of 6th month, 41 cases achieved CHR (95.3%) and the only side effect was neutropenia, two cases with grade 1, one with grade 2. One case developed blast crisis and was complicated by fatal dengue hemorrhagic fever (2.3%).

At the end of 12th month, 36 cases were still in CHR (83.7%), and the side effect was solely neutropenia, two cases with grade 1, one with grade 2. There were four patients developing blast crisis, two of these having neutropenia at the first three-month of treatment and the dose of imatinib was decreased to be 300 mg a day for adults. Two patients passed away (4.6%), one with the community-acquired pneumonia without neutropenia and one with massive intracerebral hemorrhage due to the overdose of warfarin for the concurrent valvular heart disease.

The specific genotype of BCR-ABL translocation was studied in six cases, and there appeared four cases having e14a2, one having e13a2 and one having both. The patients whose genotype was identified, were in CHR through the first year of imatinib treatment.

The complete cytogenetic response could not be established because most patients could not afford the second study of the BCR-ABL genotyping.

Discussion

Imatinib is shown to achieve and retain the CHR in 83.7% of our patients with CML-CP that seems slightly lower than 95% among the newly diagnosed CML-CP treated with imatinib 400 mg in the landmark trial[4,6] or 95% of the cases who failed to interferon alfa[7]. Many factors are presumed to contribute this figure, firstly the dose of 300 mg a day is administered in our caseswho develop neutropenia grade 1 or 2 instead of 400 mg a day, a standard dose for CML-CP in 18-year-old or older patients, and secondly, our study includes the younger age group, 3-11years, that have poorer response to imatinib. From one prospective study in France which recruited the patients with the range of 10 months to 17 years of age, complete cytogenetic response and major molecular response are found in 61% and 31% at one year of treatment, respectively[8] which are lower than 76.2% of the patients of the age group of 18-70 years of ages[4].

The common side effect of imatinib that can be found in 50 % of cases is nausea[9] but it is rarely found in our series (4.6%) moreover, our patients can continue the usual dose of imatinib without any special manipulation. Other common side effects such as superficial edema and muscle cramps are not found in our patients. The more serious side effect, neutropenia, that is totally found in 60 % of cases in the large trial with grade 3 or 4 occurring in 14 %[4], can also occur in ten cases in our series (23.2%), seven patients with grade 1 and three with grade 2, and it can completely resolve after the dose of imatinib is decreased from 400 mg to 300 mg a day.

During one year of therapy, 7 cases (16.3%) are considered an unsatisfactory response as compared

with 25% of patients who discontinued the imatinib treatment because of an unsatisfactory response and/or toxicity[10]. Of them, blastic crisis emerges in five cases (11.6%) which is slightly more than 17 cases of 283 patients (6.0%) from the study of Kantarjian et al[11], possibly because CML seems to affect the younger age group and the more patients are in the high and intermediate Sokal risk group in Asian population[12] and also the dose of imatinib is not doubled in our cases who fail to achieve CHR in the first three months or early relapse within three months after achievement of CHR[7].

There are three patients passing away, not relating to imatinib therapy (4.6%), one with dengue hemor-rhagic fever, one with the community-acquired pneu-monia without neutropenia and one with massive intracerebral hemorrhage due to the overdose of war-farin for valvular heart disease whereas the more serious side effects of imatinib, besides neutropenia, are severe heart failure[13] and hepatotoxicity[14].

Actually the cytogenetic study should have been followed within the first six months to establish the cytogenetic response, but these highly sophisticated techniques are expensive and not available in our institute, hence we use only CBC or CHR for evaluation.

Summary

The 43 patients of chronic myeloid leukemia-chronic phase with positive Philadelphia chromosome have been treated with imatinib, the first synthetic tyrosine kinase inhibitor, 300-400 mg a day. Within one year, complete hematologic response is achieved in 36 patients (83.7%) whereas four cases develop blastic crisis within few months after accessing the CHR and three cases die of non-relating to therapy. No serious side effect has been recognized during one year of treatment.

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