Original Study

Incidence of Second Malignancies of Chronic Myeloid Leukemia During Treatment With Tyrosine Kinase Inhibitors

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Abstract

To evaluate the risk of second malignancy (SM) during treatment with tyrosine kinase inhibitors (TKIs), a retrospective study was designed among chronic myeloid leukemia (CML) patients. The result suggested that patients with CML treated with TKIs had the higher relative incidence of SM compared with the expected incidence among the general Chinese population.

Background: Tyrosine kinase inhibitors (TKIs) have revolutionized the treatment of chronic myeloid leukemia (CML) by providing patients with long-term survival. Although most patients who receive TKI treatment have shown satisfactory tolerance, second malignancies (SMs) should not be ignored because of lifetime treatment. We designed a retrospective study to evaluate the incidence and possible risk factors of SMs in CML patients treated with TKIs. **Patients and Methods:** Records of 223 patients with Philadelphia chromosome-positive CML treated with imatinib were reviewed to investigate frequencies and characteristics of SMs. The data of SMs were compared with the number expected from the National Central Cancer Registry. The possible risk factors of SM in CML patients treated with TKIs were also evaluated using Poisson regression in this study. **Results:** After a median follow-up of 64 months (range, 4-253 months) from CML diagnosis, 7 patients (3.14%) developed 6 different SMs including colon, stomach, breast, kidney, cervical, and lymphonodus tissue. The risk of second cancer was higher than expected (observed-to-expected ratio, 2.45; 95% confidence interval, 1.17-5.14; $P = .018$). No associated elements were found in terms of influencing the incidence of SM in CML patients treated with TKIs. **Conclusion:** We found patients with CML treated with TKIs had a higher relative incidence of SM compared with the expected incidence among the general Chinese population. However, the correlations between second cancer and the potential risk factors including the length of exposure and cumulative dose of TKIs were not found in this study.

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Introduction

Since 1990, the prevalence of cancer has increased worldwide.[1] It is reported that cancers have been regarded as a major health-related concern in 2013. Notably, prostate cancer (1.4 million) and colon cancer (0.9 million) for men, and breast cancer (1.8 million) for women account for the highest incidence of cancer in world's population. Breast cancer, and colon and rectum cancer were the top 3 causes for disability-adjusted life-years (DALYs) and cancer death in women.[1] Differently, stomach cancer was 1 of the top 3 causes of DALYs and cancer death for men. With regard to nonsolid tumors, chronic myeloid leukemia (CML) is a quite common cancer in adults. The incidence of CML is 1.6 to 2.0/100,000 worldwide. The annual incidence ranges from 0.35 to 0.55/100,000 in China, and the median age at diagnosis is 45 to 50 years.[2-4]

The development of cancer treatment is mostly focused on targeted therapy. Targeted drugs contribute to the long-term survival of most patients, but secondary cancer is unfortunately encountered in our clinical practices. For example, tyrosine kinase inhibitors (TKIs) have revolutionized the treatment of CML by providing excellent disease control and showing satisfactory tolerance. However, several groups reported that second malignancies (SMs) of

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CML patents who received TKI treatment are of the major concern. The incidence of SM during TKI therapy was 16.0% at 10 years from 2001 to 2012 in Japanese reports.[5] Verma et al assessed 1445 patients with CML/myeloproliferative neoplasms, 66 (4.6%) patients developed 80 various second cancers.[6] In contrast, some institutions reported lower or no difference in incidence of SM than the general population.[6,7] Thus, the incidence of SMs of CML patients treated with TKIs remains divergent.

The contribution of TKI therapy to SM development is insufficiently determined to date. Some studies did not find any evidence that exposure to TKIs would increase the risk of developing second cancers.[6] However, some studies imply it can partially be explained by genomic instability in CML patients. Additionally, 1 study reported that age at initial TKI therapy had a negative correlation with the latency of development of SM.[5] Taken together, the possible risk factors for the development of SM is not clear.

We designed a retrospective study to evaluate the incidence and possible risk factors of SM in CML patients treated with TKIs. We found that patients with CML treated with TKIs had a higher relative incidence of second cancer compared with the expected incidence among the general population.

Patients and Methods

Patients and Therapy

Two hundred twenty-three Philadelphia chromosome (ph)-positive CML patients who were treated with imatinib from February 2002 to December 2011 at our institution were included in this study. All patients were treated with imatinib at a dose of 400 mg/d for chronic phase (CP) CML and 600 mg/d for advanced phase (AP)/blast phase (BP) as initial therapy. All patients signed approved informed consent in accordance with the Declaration of Helsinki.

Evaluation of Patients

Cytogenetic and molecular analyses were performed at the time of diagnosis and monitored according to European Leukemia Net criteria.[8] All patients underwent a history and physical examination, complete blood counts, and blood chemistry before the therapy and at specific time points. The time points included every month for the first 3 months, every 3 months until 12 months since the therapy, and every 6 months after 1 year. Cytogenetic response was assessed using conventional metaphase analyses with R-banding techniques[9] and molecular response was assessed using quantitative real-time polymerase chain reaction in bone marrow or peripheral blood using ABL proto-oncogene 1 (ABL) as internal control.[10] Cytogenetic and molecular response assessments were performed at baseline, every 3 months for the first 12 months, and then at least every 6 months. Response and relapse criteria were defined as previously reported.[11]

Statistical Analysis

Standardized incidence ratios (SIRs) were assessed according to methods previously described.[6] Briefly, these are the ratio of the number of patients who developed SM in our population (observed) compared with the number of expected cases from the general China population occurring in the same period time. The expected number was determined with age, sex, and calendar year-specific incidence rates from the National Central Cancer Registry (NCCR). Person-years at risk were calculated from the start of therapy with imatinib to the date of SM diagnosis, death, or date of last contact, whichever came first. The 95% confidence intervals (CIs) and P values for the SIRs were determined by assuming a Poisson distribution for the observed number of patients with subsequent cancers. Poisson regression was used for univariate and multivariate analysis. Two-sided $P < .05$ was defined as significant.

Results

At the time of last follow-up, 223 patients were enrolled in this study, including 217 in CP treated with imatinib 400 mg/d, 6 in AP or BP with 600 mg/d as initial dose. One hundred ninety-six patients received imatinib therapy only, 27 patients received first-line use of imatinib and subsequent second-generation TKIs (20 nilotinib, 7 dasatinib). Dose modification was performed in 73 patients because of tolerability (300-400 mg/d). Fifty-eight patients discontinued use of imatinib temporarily because of side effects. The median cessation time was 21 days (range, 7 days-33 months). Imatinib therapy was continued when the patients' condition became better. Their characteristics are shown in Table 1.

Seven patients developed 6 different SMs (female, n = 6; male, n = 1). Of the 7 patients with CML who developed malignancies, 5 received imatinib as front-line therapy, 2 of the patients received nilotinib after failure of imatinib treatment. Their characteristics are summarized in Tables 2 and 3.

The crude incidence rates of SMs was 3.14% (7 of 223). The SM sites included colon, stomach, breast, kidney, cervical, and lymphonodus tissue. Among these 7 patients, 2 patients developed breast cancer during imatinib therapy and the other 5 patients

Table 1 Clinical Characteristics of CML Patients With Second Cancer (n = 7)

Characteristic	Median (Range)
Age at Diagnosis of CML, Years	40 (6-78)
WBC Count at Diagnosis of CML, $\times 10^9$/L	100 (2.6-740)
Hemoglobin Level at Diagnosis of CML, g/dL	113 (44-669)
Platelet Count at Diagnosis of CML, $\times 10^9$/L	399.5 (12-4882)
Eosinophils in PB at Diagnosis of CML, %	1.5 (0-10)
Basophils in PB at Diagnosis of CML, %	1.2 (0-18)
Blast in BM at Diagnosis of CML, %	1.5 (0-9)
Eosinophils in BM at CML, %	4.5 (0-18)
Basophils in BM at Diagnosis of CML, %	2.5 (0-11)
Follow-Up After Diagnosis of CML, Months	64 (4-253)
Time From CML at Diagnosis to Second Cancer, Months	51 (13-77)
Duration of Treatment With TKIs Until Second Cancer, Months	51 (12-76)
Duration of Imatinib Treatment Until Second Cancer (n = 5), Months	55 (29-76)
Duration of Dasatinib Treatment Until Second Cancer (n = 1), Months	48
Duration of Nilotinib Treatment Until Second Cancer (n = 1), Months	12
Follow-Up After Diagnosis of Second Cancer, Months	27 (1-54)

Abbreviations: BM = bone marrow; CML = chronic myeloid leukemia; PB = peripheral blood; TKIs = tyrosine kinase inhibitors; WBC = white blood cell.