Comorbidity Increases Side Effects of Tyrosine Kinase Inhibitor in Chronic Myeloid Leukemia

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ABSTRACT:
AIM: The impact of comorbidities on side effects of tyrosine kinase inhibitors (TKIs) was investigated in CML patients.
METHODS: Total of 30 (16 male, 14 female) chronic phase chronic myeloid leukemia patients taking imatinib as initial therapy were included to the study. Charlson comorbidity index scores were calculated in patients with comorbidities. Score 0 was named group 1, score 1 and above was named group 2. One or more adverse events associated with TKI were considered as significant. Two groups were compared in terms of relationship between comorbidity and TKI side effects.
RESULTS: Median age was 57.5 years, median follow up was 42 months. Median major molecular response time (MMR) 8.5 months and median complete hematologic response time (CHR) 58 days. TKI side effects were significantly higher in patients with comorbidities (p=0.017).
CONCLUSION: According to our study, comorbidity increases TKI side effects. The occurrence of adverse drug reactions is an often unwanted condition that restricts the use of medication. Our study is important in terms of predicting and management of TKI adverse side effects in the CML patients with comorbidities.
KEYWORDS: chronic myeloid leukemia, TKI side effects, comorbidity

I. INTRODUCTION
Chronic myeloid leukemia (CML) is classified as a myeloproliferative disorder associated with the Philadelphia chromosome t(9;22)(q34;q11) resulting in a BCR-ABL fusion gene. TKIs are the initial treatment of choice for most patients with chronic phase CML (1,2). According to Feinstein definition, comorbidity is any distinct additional clinical entity pre-existent or occurring during the course of a primary disease. Comorbidities have gained in importance for choice at baseline of correct drug based on possibly associated side effects. Comorbidities have proven to have a specific role in oncology in terms of overall survival and on choice of therapeutic strategies. The Charlson comorbidity index and adult comorbidity evaluation-27 are lists of comorbidities with a weight assigned from 1 to 6 for the former and from 0 to 3 for the latter score, derived from relative risk estimates of a proportional hazard regression model using clinical data (3). Other medications and supplements that can affect the metabolism of these TKIs, lowering drug levels and thereby compromising its clinical efficacy (4).

In this study, the impact of comorbidities on side effects of TKIs was investigated in CML patients.

II. METHODS
Total of 30 patients, 16 (53.3%) male and 14 (%46.7) female, with chronic CML taking imatinib as initial therapy that followed in 2009-2013 years were evaluated retrospectively.
Patients who had CML with accelerated and blastic phases were excluded. Charlson comorbidity index scores were calculated in patients who had comorbidities. Patients having score 0 were included to the group 1 and patients having score 1 and above were included to the group 2.

Chronic phases CML was defined as the presence of all following findings in peripheral blood: blasts less than 15%, basophils less than 20%, blasts plus promyelocytes less than 30%, and platelet count over 100×10^9/L.

After diagnosis, imatinib 400 mg / day was started to the all patients. Patients were followed weekly with complete blood counts for the first 2–3 months, then every 4–6 weeks. Peripheral blood PCR was performed every three months for the first year, then every six months. Response criteria were as previously described (5,6). Briefly, a complete hematologic response (CHR) was defined as a white blood cell (WBC) count of below 10×10^9/L, a platelet count of below 450×10^9/L, absence of immature cells (blasts, promyelocytes, myelocytes) with less than 2% basophils in the peripheral blood, and disappearance of all signs and symptoms related to leukemia including palpable splenomegaly. Major molecular response (MMR) was defined as a BCR-ABL/ABL ratio of 0.1% or under (international scale) (6). TKI related side effects (edema, weight gain, dyspepsia, pleural effusion, skin rash, liver function tests, cytopenias, myalgia, arthralgia, muscle cramps, weakness, fatigue, etc.) were evaluated in each clinic visit. One or more adverse events associated with TKI were considered as significant. Overall survival is considered as time starting from diagnosis date until time of study or death due to disease or any other. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) Version 20.

III. RESULTS

The median age of the patients was 57.5 (min:27, max:87) years. In our study, mortality rate was 86.7%, and median survival was 42 months.

According to Charlson comorbidity score distribution of patients are presented in Table-1. 20 patients without comorbidities were included to the group 1 and 10 patients with one or more comorbidities were included to the group 2. The major molecular response time (MMRT), hematological response time (HRT) and survival times of two groups are shown in Table-2.

Seventeen (56.7%) patients had side effects related to the use of imatinib during their follow up time. Totally 35 side effects in these patients were recorded. Side effects were 7 edema, 4 leukopenia, 2 thrombocytopenia, 5 dyspepsia, 4 elevated liver function tests, 6 head, muscle and joint pain, 4 pleural effusion and 3 allergic rash. While medication was changed to 2nd generation TKI 8 (40%) of 17 patients with side effects; the remaining 9 patients were managed by short term imatinib interruption or addition of symptomatic therapies against to the side effects.

TKI related side effects was observed in 8 (40%) of the 20 patients in group 1 and in 9 (90%) of the 10 patients in group 2. TKI related side effects were higher in patients with comorbidities (p = 0.017).

IV. DISCUSSION

According to our study TKI side effects were significantly higher in CML patients with comorbidities. There are only limited data in the literature on the role of comorbidities in CML patients.

In most countries, physicians have more than one TKI commercially available for frontline therapy and treatment selection is made after a number of factors have been thoroughly considered, including patient’s risk scores, co-morbidities or age (7). Common side effects include myelosuppression, gastrointestinal complaints, fatigue, headache, rash, and peripheral and periorbital edema (most notably with imatinib) (8,9). Chronic, low-grade toxicities from tyrosine kinase inhibitors affect the quality of life of some patients with CML, and symptoms should be made to reduce or eliminate them whenever possible. A survey-based study evaluated health-related quality of life (HRQOL) in 448 patients with CML treated with imatinib for a median of five years (10,11). Older patients (>60 years) had HRQOL scores similar to age-matched persons in the general population, while younger patients reported significantly worse HRQOL (12-15). Comorbidities have gained in importance for choice at baseline of correct drug based on possibly associated side effects. According to Feinstein definition, comorbidity is any distinct additional clinical entity pre-existent or occurring during the course of a primary disease (16). Comorbidities have proven to have a specific role in oncology in terms of overall survival and on choice of therapeutic strategies (17-19). It has been reported on a large retrospective database of more than 1800 CML patients, that 88% of these had more than one comorbidity at baseline and 63% of patients assumed more than 1 drug not related to CML. Each agent used for treatment of CML is associated to a specific safety profile that may contraindicate use of one drug over another for selected categories of patients (20). Other study reported that obesity at baseline predisposing to slow cytogenetic and molecular responses in imatinib-treated patients: however, this comorbidity, and related hyperglycemia and dyslipidemia, should be taken into account for possible associated events in patients treated with second generation tyrosine kinase inhibitors (21).
Doctors and patients may worry about the side effects due to drugs in order to determine treatment strategies during the treatment of CML (psychological burden of a lifelong treatment the patient. According to our study, determining the importance of comorbidities among TKI side effects may help us to be prepared and to make appropriate strategies for patients with CML. There is a need for further research about this issue.

Table 1: The distribution of patients according to comorbidity scores

<table>
<thead>
<tr>
<th>Comorbidity score</th>
<th>Number (%)</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>20 (66.7%)</td>
</tr>
<tr>
<td>1</td>
<td>7 (23.3%)</td>
</tr>
<tr>
<td>2</td>
<td>2 (6.7%)</td>
</tr>
<tr>
<td>3</td>
<td>1 (3.3%)</td>
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Table 2: The distribution of two groups according to age, MMR, CHR and survival times

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>59 (27-87)</td>
<td>51.5 (31-85)</td>
</tr>
<tr>
<td>MMR time median (range)*</td>
<td>8.5 (0-18)</td>
<td>10 (0-18)</td>
</tr>
<tr>
<td>CHR time, median (range)**</td>
<td>55 (30-180)</td>
<td>58 (0-90)</td>
</tr>
<tr>
<td>Survival, median (range)***</td>
<td>42 (16-82)</td>
<td>43.5 (13-65)</td>
</tr>
</tbody>
</table>

*month
**day

REFERENCES

[7]. Sánchez-Gujo F. Elderly CML patients' treatment: considering not only physician's judgment but also co-morbidity indexes. Leuk Res. 2014;38:1156-1157.
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