Pulmonary Hypertension Is a Frequent Event in Patients with Chronic Myeloid Leukemia Treated with Tyrosine Kinase Inhibitors

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Pulmonary Hypertension Is a Frequent Event in Patients with Chronic Myeloid Leukemia Treated with Tyrosine Kinase Inhibitors

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Abstract

Tyrosine kinase inhibitors (TKIs) are the current standard therapy for patients with chronic myeloid leukemia (CML). Right heart failure and pleural effusions have been reported in patients treated with TKIs, particularly with dasatinib. Although TKIs have been shown to induce pulmonary hypertension (PH), there have been no studies addressing the prevalence of PH in patients treated with these TKIs. We conducted a retrospective analysis of 64 patients diagnosed with CML in chronic phase (CP) who were treated with TKIs (dasatinib, nilotinib, or imatinib) as initial therapy for CML. To investigate the frequency and characteristics of PH in these patients, we conducted a chart review of patients with CML treated with TKIs (imatinib, dasatinib, or nilotinib) during the course of therapy. The improvement in RVSP was seen after switching from the TKI to another agent (Dasatinib n=2, nilotinib n=1) or reducing the dose of dasatinib by 50% (N=1). In 10 patients (18%), pleural effusion was identified before starting therapy with nilotinib. Pleural effusion was identified in 11 patients (55%) with elevated RVSP (suggesting PH) (Table 3). Further investigation is needed to fully characterize the relationship between TKIs and the development of PH.

Background

• Pulmonary hypertension (PH) is characterized by elevated pulmonary artery pressures, right ventricular hypertrophy and, eventually, right ventricular failure.

• Unexplained PH has been described in some myeloproliferative disorders, however evidence is lacking in patients with CML.

• There have been some reports on the occurrence of reversible PH after treatment with dasatinib.

Objective

• To investigate the frequency and characteristics of PH in patients with CML receiving therapy with tyrosine kinase inhibitors (TKIs).

Patients and Methods

• Chart review of patients with CML treated with TKIs at MDACC between 2000 and 2009.

• Included patients with CML in chronic phase (CP) enrolled in several studies using imatinib (800mg orally daily), nilotinib (400mg BD) or dasatinib (100mg orally daily) as front-line therapy who had at least one transthoracic echocardiogram (TTE) done at some point during the course of therapy. The improvement in RVSP was seen after switching from the TKI to another agent (Dasatinib n=2, nilotinib n=1) or reducing the dose of dasatinib by 50% (N=1).

• Patients with CML CP who had received prior TKI therapy are occasionally...

Results

• Of the patients that had elevated RVSP (suggesting PH), 13 patients had serial TTE during therapy (figure 1).

• 7 patients experienced worsening PH (reducing Dasatinib n=2, Nilotinib n=3).

• 4 had resolution (reducing imatinib n=2, Dasatinib n=3, nilotinib n=1) while on therapy.

• The improvement in RVSP was seen after switching from the TKI to another agent (Dasatinib n=2, nilotinib n=1) or reducing the dose of dasatinib by 50% (N=1).

• Only 4 of 54 (8%) patients treated with imatinib had elevated RVSP (Table 3).

Conclusions

• PH occurs in some patients with CML in chronic phase at baseline while in others it appears during therapy with TKI.

• PH is seen less commonly in patients on imatinib compared to dasatinib or nilotinib.

• Concomitant pleural effusion and PH occurred more frequently in patients receiving dasatinib.

• Unclear whether there is a causal relationship between TKI and PH.

• A larger prospective study is needed to further investigate the relationship between TKIs and the development of PH.

References:


Table 1. Patient's Characteristics

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Median (range)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>56 (30-88)</td>
<td>11 (50)</td>
</tr>
<tr>
<td>Females</td>
<td>59 (28-84)</td>
<td>17 (51)</td>
</tr>
</tbody>
</table>

Table 2. TTE evidence of PH by therapy

<table>
<thead>
<tr>
<th>TKI used</th>
<th>N TTE Available</th>
<th>N Elevated RVSP on TTE (%)</th>
<th>N Possible secondary cause of elevated RVSP</th>
</tr>
</thead>
<tbody>
<tr>
<td>imatinib</td>
<td>54 (4/8)</td>
<td>2/12 (17%)</td>
<td>1/9 (11%)</td>
</tr>
<tr>
<td>dasatinib</td>
<td>19 (10/53)</td>
<td>2/10 (20%)</td>
<td>1/9 (11%)</td>
</tr>
<tr>
<td>nilotinib</td>
<td>14 (6/43)</td>
<td>2/5 (40%)</td>
<td>1/9 (11%)</td>
</tr>
</tbody>
</table>

Table 3. Incidence of pleural effusion

<table>
<thead>
<tr>
<th>TKI used</th>
<th>N Concomitant PE and RVSP</th>
<th>N of patients with SOB</th>
</tr>
</thead>
<tbody>
<tr>
<td>imatinib</td>
<td>3/4 (75%)</td>
<td>1</td>
</tr>
<tr>
<td>dasatinib</td>
<td>7/10 (70%)</td>
<td>4</td>
</tr>
<tr>
<td>nilotinib</td>
<td>1/6 (17%)</td>
<td>0</td>
</tr>
</tbody>
</table>

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