Pregnancy Outcomes Among Patients with Chronic Myeloid Leukemia Treated with Dasatinib

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Pregnancy outcomes during dasatinib treatment

Background (1)

Chronic myeloid leukemia

- Chronic myeloid leukemia (CML) is a clonal stem-cell disorder of the bone marrow
  - caused by Bcr-Abl, a chimeric tyrosine kinase formed by a chromosomal translocation, t(9;22)(q34;q11.2)\(^1,2\)
  - can affect patients of all ages, including those of child-bearing potential\(^3\)

- The first-line therapy is imatinib, a tyrosine kinase inhibitor (TKI)
  - some patients may develop resistance or intolerance to imatinib
Background (2)

Dasatinib

- Dasatinib (SPRYCEL®) is a second-line TKI targeting Bcr-Abl
- Indicated in the treatment of all phases of CML or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) in patients resistant to or intolerant of previous treatment, including imatinib\(^4-8\)
- Clinical and preclinical efficacy has been shown across all tested mutations, except T315I\(^9\)
- Active against a broad range of other resistance mechanisms
Background (3)

TKIs and pregnancy

- All commercially available TKIs are potentially teratogenic; fetal toxicity observed in rodents, but the effect on humans is unclear\textsuperscript{10-12}
  - pregnancy was an exclusion criteria during clinical trials of all available TKIs
  - although taking TKIs while pregnant is not recommended, some patients have become pregnant

- Survey of imatinib case studies: known outcomes for approximately 125 women\textsuperscript{13,14}
  - 50% delivered normal infants
  - 28% terminated pregnancies (3 following detection of abnormalities)
  - 14% had spontaneous abortions
  - 7% (8 live births, 1 stillbirth) had infants with abnormalities

- Adequate contraception should be used; if pregnancy occurs, the potential hazard to the fetus should be discussed with the patient\textsuperscript{10-12}
Pregnancy outcomes during dasatinib treatment

Study objectives

- To assess, using case studies from clinical trials and postmarketing reports, the effects of dasatinib on
  - pregnant female patients
  - pregnant partners of male patients receiving dasatinib at conception
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Methods

- Data was obtained via
  - clinical study reports for 16 patients in phase I–III dasatinib trials
  - post-marketing surveillance compiled from 6 voluntarily submitted reports from community physicians; full medical details are not available in these cases

- Estimated worldwide patient exposure
  - clinical trials: more than 3,000 patients have been treated with dasatinib in clinical trials
  - marketed: more than an estimated 6,000 patients have received dasatinib since marketing began*

*There is no readily available information on the actual number of patients treated with dasatinib. The number of patients worldwide treated with dasatinib is derived from sales figures, an approximation of the total quantity sold. The estimated sales and average dose and duration of treatment (based on the prescribing information) are used to calculate the approximate number of patients treated
Results (1)

Baseline characteristics

- To date, 13 female patients have been identified as becoming pregnant while receiving therapy with dasatinib

- In addition, 9 male patients have conceived children while receiving therapy with dasatinib

- Baseline characteristics for male and female patients are shown in Table 1
Table 1a. Baseline characteristics for female patients

<table>
<thead>
<tr>
<th>Identifier</th>
<th>Age</th>
<th>Disease</th>
<th>Prior pregnancy history</th>
<th>Months on drug at presentation of pregnancy</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient A</td>
<td>39</td>
<td>CML</td>
<td>NR</td>
<td>3</td>
<td>Obesity, multiple abdominal surgeries</td>
</tr>
<tr>
<td>Patient B</td>
<td>36</td>
<td>CML</td>
<td>NR</td>
<td>1</td>
<td>Uncontrolled CML; extreme thrombocytopenia; previous hydroxyurea treatment</td>
</tr>
<tr>
<td>Patient C</td>
<td>28</td>
<td>CML</td>
<td>G0, P0</td>
<td>12</td>
<td>Multiple concomitant medications</td>
</tr>
<tr>
<td>Patient D</td>
<td>38</td>
<td>CP-CML</td>
<td>G1, P1</td>
<td>10</td>
<td>Neutropenia; tobacco use; multiple concomitant medications including intramuscular contraceptive</td>
</tr>
<tr>
<td>Patient E</td>
<td>33</td>
<td>CML</td>
<td>G3, P3</td>
<td>30</td>
<td>Alcohol and tobacco use; obesity</td>
</tr>
<tr>
<td>Patient F</td>
<td>36</td>
<td>CML</td>
<td>G3, P2</td>
<td>15</td>
<td>Multiple concomitant medications; sickle cell anemia; pain crisis during pregnancy</td>
</tr>
</tbody>
</table>

NR = Not reported
## Table 1a. Baseline characteristics for female patients

<table>
<thead>
<tr>
<th>Identifier</th>
<th>Age</th>
<th>Disease</th>
<th>Stage of pregnancy</th>
<th>Months on drug at presentation of pregnancy</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient G</td>
<td>29</td>
<td>AP-CML</td>
<td>G2, P2</td>
<td>4</td>
<td>Multiple concomitant medications</td>
</tr>
<tr>
<td>Patient H</td>
<td>NR</td>
<td>CML</td>
<td>G0, P0</td>
<td>5</td>
<td>None</td>
</tr>
<tr>
<td>Patient I</td>
<td>28</td>
<td>CP-CML</td>
<td>NR</td>
<td>9</td>
<td>NR</td>
</tr>
<tr>
<td>Patient J</td>
<td>21</td>
<td>CML</td>
<td>G0, P0</td>
<td>30</td>
<td>None</td>
</tr>
<tr>
<td>Patient K</td>
<td>24</td>
<td>CP-CML</td>
<td>G5, P5</td>
<td>8</td>
<td>Iron-deficient anemia</td>
</tr>
<tr>
<td>Patient L</td>
<td>23</td>
<td>CP-CML</td>
<td>G4, P2</td>
<td>1</td>
<td>Prev. stillbirth/spont. abortion</td>
</tr>
<tr>
<td>Patient M</td>
<td>18</td>
<td>CML</td>
<td>NR</td>
<td>8</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR = Not reported
# Pregnancy outcomes during dasatinib treatment

## Table 1b. Baseline characteristics for male patients

<table>
<thead>
<tr>
<th>Identifier</th>
<th>Age</th>
<th>Disease</th>
<th>Time on drug (months)</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient N</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Unknown</td>
</tr>
<tr>
<td>Patient O</td>
<td>38</td>
<td>CP-CML</td>
<td>12</td>
<td>Previous cytarabine therapy; partner on oral contraceptive ethinylestradiol</td>
</tr>
<tr>
<td>Patient P</td>
<td>34</td>
<td>CP-CML</td>
<td>6</td>
<td>Previous therapy with hydroxyurea, anagrelide; multiple concomitant medication including influenza vaccine</td>
</tr>
<tr>
<td>Patient Q</td>
<td>43</td>
<td>BC-CML</td>
<td>10</td>
<td>Anemia; bleeding tendency; prior hydroxyurea therapy; concomitant antibiotics</td>
</tr>
<tr>
<td>Patient R</td>
<td>32</td>
<td>CML</td>
<td>NR</td>
<td>History of GVHD; ex-tobacco use; prior hydroxyurea, interferon, and cytarabine therapy</td>
</tr>
</tbody>
</table>

NR = Not reported
Pregnancy outcomes during dasatinib treatment

Table 1b. Baseline characteristics for male patients

<table>
<thead>
<tr>
<th>Identifier</th>
<th>Age</th>
<th>Disease</th>
<th>Time on drug (months)</th>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient S</td>
<td>41</td>
<td>CML</td>
<td>7</td>
<td>Psoriasis; sleep apnea; prior interferon therapy; multiple concomitant medications</td>
</tr>
<tr>
<td>Patient T</td>
<td>49</td>
<td>CP-CML</td>
<td>8</td>
<td>Age; alcohol and tobacco use; concomitant furosemide and lorazepam</td>
</tr>
<tr>
<td>Patient U</td>
<td>NR</td>
<td>NR</td>
<td>1</td>
<td>NR</td>
</tr>
<tr>
<td>Patient V</td>
<td>24</td>
<td>CML</td>
<td>1</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR = Not reported
Pregnancy outcomes during dasatinib treatment

Selected cases of female patients electing to carry

Patient D

- 38 years old; CP-CML; G1, P1
- Time on therapy: 180 mg/day for 9.5 months
- Duration of fetal exposure: 5 weeks
- Additional information: experienced nonserious depression, agitation, fever, neutropenia, petechiae, fatigue, muscle pain, oral cavity hemorrhage, and chest pain during pregnancy
- Outcome: spontaneous abortion at 8 weeks (no birth defects); no adverse maternal reaction
- Disease status at cessation of dasatinib: not reported
- Disease status at time of delivery: not reported
- Duration before postdelivery treatment resumption: 12 days
Patient E

- 33 years old; CP-CML, unknown phase; G3, P3
- Time on therapy: 100 mg once daily for 30 months
- Duration of fetal exposure: 9 weeks
- Additional information: history of tobacco and alcohol use
- Outcome: spontaneous abortion at 9 weeks; no adverse maternal reaction
- Disease status at cessation of dasatinib: not reported
- Disease status at time of delivery: not reported
- Duration before postdelivery treatment resumption: not reported
Pregnancy outcomes during dasatinib treatment

Selected cases of female patients electing to carry (cont’d)

Patient F

- 36 years old; CP-CML, chronic phase; G3, P2
- Time on therapy: 70 mg twice daily for 15 months
- Duration of fetal exposure: 7 weeks; patient also treated with hydroxyurea and interferon throughout pregnancy
- Outcome: delivered a live, normal infant; no adverse maternal reaction
- Disease status at cessation of dasatinib: not reported
- Disease status at time of delivery: progression of CML 3 months after cessation of dasatinib therapy; status remained the same at the time of delivery
- Duration before postdelivery treatment resumption: not reported
Pregnancy outcomes during dasatinib treatment

Selected cases of female patients electing to carry (cont’d)

Patient G

- 29 years old; AP-CML; G2, P2
- Time on therapy: 70 mg twice daily for 4 months
- Duration of fetal exposure: unknown
- Additional information: Apgar scores unknown; compliance unknown prior to pregnancy
- Outcome: delivered a live infant by C-section at 7 months’ gestation – ‘small for dates’, but without obvious defects; reason for C-section is unknown; patient died of blast-phase CML 4 months postdelivery
- Disease status at cessation of dasatinib: not reported
- Disease status at time of delivery: not reported
- Duration before postdelivery treatment resumption: not reported
Pregnancy outcomes during dasatinib treatment

Selected cases of female patients electing to carry (cont’d)

Patient H

- Age and CML stage unknown; G0, P0
- Time on therapy: 100 mg once daily for 5 months
- Duration of fetal exposure: 21 days
- Outcome: unknown
- Disease status at cessation of dasatinib: not reported
- Disease status at time of delivery: not reported
- Duration before postdelivery treatment resumption: not reported
Pregnancy outcomes during dasatinib treatment

Selected cases of female patients electing to carry (cont’d)

Patient I

- 28 years old; CP-CML; G0, P0
- Time on therapy: 50 mg twice daily for 9 months
- Duration of fetal exposure: 6 weeks
- Outcome: unknown
- Disease status at cessation of dasatinib: not reported
- Disease status at time of delivery: not reported
- Duration before postdelivery treatment resumption: not reported
Pregnancy outcomes during dasatinib treatment

Selected cases of female patients electing to carry (cont’d)

Patient J

- 21 years old; CP-CML; G0, P0
- Time on therapy: 100 mg once daily 2.5 years
- Duration of fetal exposure: 6 weeks
- Outcome: unknown
- Disease status at cessation of dasatinib: not reported
- Disease status at time of delivery: not yet delivered
Pregnancy outcomes during dasatinib treatment

Selected cases of female patients electing to carry (cont’d)

Patient K

- 24 years old; CP-CML; G5, P5
- Time on therapy: 100 mg once daily for 8 months
- Duration of fetal exposure is unknown
- Additional information: had 5 children previously with no congenital abnormalities; no previous abortions/stillbirths
- Outcome: unknown
- Disease status at cessation of dasatinib: not reported
- Disease status at time of delivery: not yet delivered
Results (2)

Outcomes of female case studies

- 13 patients:
  - normal newborn: 1 patient
  - ‘small for dates’ newborn: 1 patient
  - induced abortion: 4 patients (patient’s decision)
  - spontaneous abortion: 2 patients
  - pregnant at last follow-up: 5 patients
  - all patients ceased dasatinib after discovery of pregnancy
Results (3)

Outcomes of male case studies

- Age range: 22–49 yrs
- Diseases: CP-CML, BC-CML, unknown phase CML
- Time on therapy (range): 1 month to more than 12 months
- Complicating factors: most patients took multiple concomitant medications
- Outcome available for 7/9 patients: normal, healthy infants born to partners in all cases
Conclusions

- The data from these patients indicate that
  - infants from female patients who took dasatinib during pregnancy and were carried to term exhibited no abnormalities
  - infants from partners of male patients who took dasatinib during conception did not exhibit abnormalities

- Although there were no apparent fetal abnormalities, fetal risk cannot be excluded
  - women should be advised of the potential hazard to the fetus and to avoid becoming pregnant if taking dasatinib
  - if dasatinib is used during pregnancy or if the patient becomes pregnant while taking dasatinib, the patient should be apprised of the potential hazard to the fetus
References

10. Imatinib Prescribing Information
11. Nilotinib Prescribing Information
12. Dasatinib Prescribing Information
Footnotes

Acknowledgment

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Disclosures

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