Author's response to reviews

Title: Gynecomastia during imatinib mesylate treatment for gastrointestinal tumor: a rare adverse event

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Author's response to reviews: see over
Aug. 14, 2011

Dear editor:

Thank you very much for your consideration of our manuscript entitled "Gynecomastia during imatinib mesylate treatment for gastrointestinal tumor: a rare adverse event".

We have revised our manuscript according to the requirement of the journal and referees. The changed parts of the manuscript were highlighted with red color in revised manuscript.

Sincerely,

Prof. ZS Yan
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The authors’ answers to the questions:

**Referee 1 (Prof. Giovanni Caocci):**

**Major compulsory revisions:**

**Question 1:** Full spectrum of steroid hormones and stimulating hormones (as published by Gambacorti et al.) before and after tamoxifene treatment should be provided: in particular, if possible, 17-OHP levels.

**Answer:** Five in the six gynecomastia patients were given tamoxifene. The other one patient didn’t be given tamoxifene because he suffered from hepatitis B. The follicle-stimulating hormone (FSH), luteinising hormone (LH), 17-hydroxyprogesterone (17-OHP), testosterone, and estradiol were assayed in 5 patients before and after tamoxifene treatment. As showed in the table. Through pared t test we found that all sex hormones had no significant changes before and after tamoxifene treatment ($P>0.05$).

<table>
<thead>
<tr>
<th>Gynecomastia Age</th>
<th>Before Tamoxifene</th>
<th>After Tamoxifene</th>
<th>Before Tamoxifene</th>
<th>After Tamoxifene</th>
<th>Before Tamoxifene</th>
<th>After Tamoxifene</th>
<th>Before Tamoxifene</th>
<th>After Tamoxifene</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 35</td>
<td>7.0</td>
<td>8.2</td>
<td>8.2</td>
<td>7.8</td>
<td>574.6</td>
<td>582.4</td>
<td>27.0</td>
<td>26.6</td>
</tr>
<tr>
<td>2 70</td>
<td>3.2</td>
<td>4.0</td>
<td>6.6</td>
<td>7.3</td>
<td>384.2</td>
<td>375.6</td>
<td>43.8</td>
<td>44.2</td>
</tr>
<tr>
<td>3 76</td>
<td>8.5</td>
<td>7.5</td>
<td>3.0</td>
<td>4.0</td>
<td>356.6</td>
<td>366.1</td>
<td>71.2</td>
<td>75.0</td>
</tr>
<tr>
<td>4 75</td>
<td>5.9</td>
<td>6.2</td>
<td>4.6</td>
<td>4.5</td>
<td>385.1</td>
<td>392.4</td>
<td>51.0</td>
<td>49.3</td>
</tr>
<tr>
<td>5 54</td>
<td>11.0</td>
<td>9.4</td>
<td>3.5</td>
<td>5.0</td>
<td>369.5</td>
<td>350.2</td>
<td>29.3</td>
<td>31.2</td>
</tr>
<tr>
<td>6☆ 49</td>
<td>9.3</td>
<td>NA</td>
<td>5.4</td>
<td>NA</td>
<td>381.4</td>
<td>NA</td>
<td>34.9</td>
<td>NA</td>
</tr>
</tbody>
</table>

* Normal value 1.5—12.5IU/L  
# Normal value 1.7—8.6IU/L  
※ Normal value 241.0-847.0ng/dl  
§ Normal value 11.6-41.2 pg/ml  
▲ Normal value 0.6-5.4 nmol/L  
NA: not assayed.

☆ The patient suffered from hepatitis B and tamoxifene was not given to him.
Question 2: The potential impact of first and second generation TKI on gynecomastia should be discussed (not only imatinib)

Answer: First-line tyrosine kinase inhibitor (TKI) therapy with imatinib has resulted in dramatic clinical response in patients with chronic myeloid leukemia (CML) or gastrointestinal stromal tumor (GIST). However, despite the excellent results, many imatinib-treated patients discontinue therapy due to an inadequate response or toxicity. Second-generation TKI (2G-TKI), such as sunitinib, dasatinib and nilotinib, can be effective after failure of imatinib treatment. The second generation TKIs are multtargeted inhibitors. In fact, dasatinib exerts a more potent inhibitory action on c-Kit and PDGFR. c-kit, PDGFR-α and PDGFR-β are important signal transduction modulators in testis organogenesis, Leydig’s cell differentiation and recruitment, spermatogenesis and steroidogenesis. So the possibility of gynecomastia caused by second generation TKIs exists. As expected, Prof. Caocci reported a male patient suffered gynecomastia after treatment with dasatinib for CML. Recently, there was a case report of gynecomastia developed after treating renal cancer with sunitinib. (in page 7 of revised manuscript)

Minor essential revisions:

1. Abstract: In the results section it is not clear to which patients the authors are referring when they speak about serum free testosterone levels (those with or without gynecomastia?)
Answer: We referred patients with gynecomastia, and indicated in the revised manuscript. (in page 2 of revised manuscript)

2. Introduction: please also consider the reported relationship between Dasatinib and gynecomastia.
Answer: Yes, we have added the content about the relationship between Dasatinib and gynecomastia which reported by Prof. Caocci in 2008. (in page 3 of revised manuscript)

3. Please provide schedule and duration of tamoxifene treatment.
Answer: Tamoxifene citrate was given 20mg per day, duration is 8 to 27 weeks. (in page 5 of revised manuscript)
4. Also provide any additional medication with the potential to influence hormonal levels by interacting with imatinib (e.g., spironolactone)

**Answer:** Some medications, such as spironolactone, indeed have the potential to influence hormone levels, even induce gynecomastia. Spironolactone can block androgen production, blocking androgens from binding to their receptors, and increasing both total and free estrogen levels. Production of testosterone is decreased by inhibiting 17-hydroxylase and 17,20-desmolase, which are enzymes in the testosterone synthesis pathway.

During the course of imatinib mesylate treatment, there were three GIST patients occasionally received low dose spironolactone (20mg daily) for periorbital edema, but gynecomastia did not happen to these three patients. (in page 6 of revised manuscript)

5. Alternative treatments of gynecomastia should be discussed, e.g. radiation, considering the interaction of tamoxifene with imatinib.

**Answer:** Three forms of treatment have been used effectively to alleviate or prevent the development of gynecomastia and/or breast pain: radiation, surgery, and medical therapy. (1) Radiationtherapy can provide effective relief from breast pain due to gynecomastia, although it has minimal effect on breast size.(2) Most cases of gynecomastia can be surgically treated by a subcutaneous mastectomy through an areolar or periareolar incision. Another recently employed technique is endoscope-assisted mastectomy, which offers the potential to reduce further scarring.(3) Androgens, antiestrogens, aromatase inhibitors, and danazol have been used to treat gynecomastia. In our practice, surgery and radiation have been used less often for this entity.

Imatinib metabolized in vivo mainly through CYP3A4, and tamoxifene is a substrate of CYP3A4. The concomitant use of two drugs may enhance the effects of tamoxifene.(in page 8 of revised manuscript)
Referee 2 (Prof. Philippe Cassier):

Minor essential revisions:

1. authors should consider rephrasing some sentences.

Answer: Yes, we have rewritten some sentences as showed in red color in the revised manuscript.

2. The author state in their introduction that gynecomastia is a rare event in patients treated with imatinib mesylate which is in line with the reviewer’s personal experience, although as it is rarely symptomatic it may be underreported. However, in the material and methods and result section it appears that 6 of 57 (10%!!!) had such an event therefore making it a very frequent side effect, especially considering that all patients apparently complained about their gynecomastia being painful. Please discuss hypotheses possibly explaining this difference between expected and observed frequency.

Answer: We have same feeling that the gynecomastia is a rare event during the patients treated with imatinib. But the actual incidence of the side effect is high. Gambacorti-Passerini et al reported in 2003 that 38 men receiving imatinib for chronic myeloid leukaemia and found 7 cases of gynecomastia (18.4%). There are two reasons for the difference between expected and observed frequency. The first reason is the patient feel shy if they report this discomfort to doctor, so they always conceal this discomfort if the doctor doesn’t ask about it. The second reason is the physicians apt to ignore this side effect when the physicians perform regular physical examination and don’t use sonography. On the contrary, we surgeons maybe more sensitive to the changes of surgical condition. (in page 7 of revised manuscript)

3. As the authors underline in their discussion, other medications are known to cause gynecomastia, it is therefore essential that the authors a list of concurrent medications taken by their patients.

Answer: There were no other special medications taken by our patients except that three patients received low dose spironolactone (20mg daily) when they were found having periorbital edema, but gynecomastia didn’t happen to the three patients. (in
Referee 3 (Prof. Vincenzo Pitini):

We are grateful to Prof. Vincenzo Pitini for his/her support and encouragement.