Dasatinib Induces a Response in Malignant Thymoma

TO THE EDITOR: Dasatinib is a novel, oral, multitargeted kinase inhibitor of Bcr-Abl and Src family kinases, as well as ephrin receptor kinases, platelet-derived growth factor receptor, and c-Kit.1 It was recently shown to be effective in inducing hematologic and cytogenetic responses in imatinib-resistant BCR-ABL-positive leukemias.2 Preclinical studies have also revealed that dasatinib has activity in head and neck, lung, pancreatic, and prostate cancer cells, raising the possibility that dasatinib may have a wider spectrum for other clinical diseases.3-6

We report, in this letter, the first clinical case of a dasatinib-responsive thymoma. The patient was diagnosed with chronic myeloid leukemia in 1994 and developed lymphoid blast crisis in 2003 after interferon-alfa therapy. He was treated with imatinib and conventional chemotherapy and achieved a complete cytogenetic remission (CCR). He was maintained on imatinib and remained in CCR. In October 2005, he developed another lymphoid blast crisis with white cell counts of 17,840/mm³, blasts 86%, hemoglobin 5.9 g/dL, and platelet counts of 5,000/mm³. Direct sequencing of the Abl kinase revealed the Y253H mutation. A chest x-ray showed a left hilar mass and left pleural effusion. Computer tomography (CT) of the thorax confirmed the presence of the anterior mediastinal mass with a volumetric measurement of 69.3 cm³. Cytologic examination of the effusion revealed a predominant lymphocytic yield. Severe thrombocytopenia precluded a biopsy of the mass. He was enrolled onto the local internal review board approved phase II dasatinib clinical trial and started on 140 mg daily in November 2005. Two months after dasatinib, he achieved a complete hematologic and cytogenetic remission. CT of the thorax showed a partial resolution in the size of the mediastinal mass (40.6 cm³) but worsening of the pleural effusion, a possible dasatinib-related adverse effect (Fig 1). His thrombocytopenia had resolved and a thoracotomy was performed to drain the pleural fluid and the mass was completely resected.

The thymic tumor (Fig 2A) featured lobular, organotypic proliferation of neoplastic epithelial cells, with large vesicular nuclei and prominent nucleoli, admixed with a background population of small lymphocytes. There were occasional perivascular spaces and scattered macrophages. Cystic degeneration accompanied by hemorrhage and siderophages was prominently displayed. Although there were lymphocyte poor areas where the tumor cells appeared to form more confluent sheets, the nuclear features remained those of B2-type. The tumor had infiltrated into but not through the capsule (modified Masaoka stage I). Leukemic infiltrates were not seen. The tumor cells were evaluated for their cell membrane reactivity with epidermal growth factor receptor (EGFR) using the anti-EGFR mouse monoclonal antibody (clone E30; DakoCytomation, Glostrup, Denmark). The guidelines of the College of American Pathologists for HER2/cerb-B2 were used to grade EGFR membrane expression. EGFR cell membrane staining of a score of 1+ (faint incomplete) to 2+ (moderate but complete) was detected in 20% of the tumor cells (Fig 2B). The

![Fig 1. The (A1, A2) top two panels were taken at the level just below the carina and the (B1, B2) bottom panels were taken at the level of the right pulmonary artery. The images on the (A1, B1) left were taken in October 2005 and images on the (A2, B2) right were taken in January 2006.](image-url)
tumor cells were negative for c-KIT membrane staining with the rabbit antihuman CD117 polyclonal antibody (DakoCytomation). These findings of EGFR positivity and c-KIT negativity were consistent with previous reports of tyrosine kinase expression in thymomas. The tumor tissue was also subjected to fluorescence in situ hybridization (FISH) analysis using the dual-color LSI EGFR/CEP 7 probe (Vysis, Downers Grove, IL; Fig 2C). A total of 60 cells were enumerated. The average number of EGFR signals per cell was 3.2, giving an average ratio of EGFR to chromosome 7 centromere signal of 1.53. This was higher than the minimum ratio of 1.3, proposed by Ionescu et al9 as the definition of EGFR gene amplification, suggesting that the thymoma did have amplification of EGFR. FISH using the LSI BCR/ABL1 dual fusion translocation probe in conjunction with the LSI ASS confirmed that the fusion BCR/ABL1 signal was absent in all 200 nuclei enumerated. Pleural biopsy revealed fibrosis and chronic inflammation.

Possible mechanisms of action leading to this clinical response include the inhibition of Src, EGFR, or Arg tyrosine kinases by dasatinib. The biologic interactions between Src and EGFR have been well characterized. These involve the physical association of Src with EGFR resulting from ligand activation of EGFR, tyrosine phosphorylation on EGFR by Src, and regulation of EGFR degradation by Src. Because dasatinib inhibits the kinase activity of Src and EGFR, it is possible that EGFR activity may be inhibited directly and/or indirectly, the latter through Src inhibition. A recent study showed that dasatinib was able to induce apoptosis in EGFR-dependent lung cancer cells and Src inhibition was thought to play a role. The Src kinases, Lck and Fyn, are important in T cell and thymic development. It is therefore conceivable that inhibition of these kinases may also contribute to the observed response. Dasatinib is also a potent inhibitor of Arg tyrosine kinase at nanomolar concentrations (F. Lee, Bristol-Myers Squibb, personal communication, March 2006). Arg tyrosine kinase has been shown to be overexpressed in thymomas and the expression is correlated with stage. Although the thymoma in this case was stage I, Arg kinase inhibition could still be involved in the response seen.

Further studies should be carried out to understand and define the biologic mechanisms by which the thymoma responded to dasatinib. Clinical trials should also be conducted to confirm this observation and will potentially benefit patients especially those who have unresectable masses or who are unfit for surgery.

Charles Chuah, Tse Hui Lim, Alvin Soon Tiong Lim, and Sim Leng Tien
Singapore General Hospital, Singapore, Singapore

Chong Hee Lim
National Heart Centre, Singapore, Singapore

Richie Soong
National University of Singapore, Singapore

Francis Lee
Bristol-Myers Squibb, Princeton, NJ

Yeh Ching Linn, Yeow Tee Goh, Foong Koon Cheah, and Alwin Hwai Liang Loh
Singapore General Hospital, Singapore, Singapore

REFERENCES


8. Pan CC, Chen PC, Chiang H: KIT (CD117) is frequently overexpressed in thymic carcinomas but is absent in thymomas. J Pathol 202:375-381, 2004

Fig 2. (A) Neoplastic epithelial cells of type B2 thymoma with vesicular chromatin and distinct nucleoli admixed with lymphocytes (hematoxylin and eosin, original magnification ×400). (B) Partial and complete cell membrane staining for epidermal growth factor receptor (EGFR). (C) LSI EGFR/CEP7 dual color probe (Vysis, Downers Grove, IL) showing five copies of the EGFR gene (red signals) and two copies of chromosome 7 (green signals).

DOI: 10.1200/JCO.2006.08.8963

Authors’ Disclosures of Potential Conflicts of Interest

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

<table>
<thead>
<tr>
<th>Authors</th>
<th>Employment</th>
<th>Leadership</th>
<th>Consultant</th>
<th>Stock</th>
<th>Honoraria</th>
<th>Research Funds</th>
<th>Testimony</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charles Chuah</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bristol-Myers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Francis Lee</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Squibb</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>