Experience with $^{90}$Y-ibritumomab tiuxetan for relapsed classical Hodgkin lymphoma

Both non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL) are radiosensitive tumors. The efficacy of radioimmunotherapy (RIT) targeting tumor-associated CD20 antigen has been established in several types of B-cell NHL. Although the malignant Hodgkin and Reed–Sternberg (HRS) cells of classical HL are of B-cell origin, they infrequently express CD20 antigen and therefore cannot be effectively targeted by anti-CD20 mAbs [1–6]. However, because the microenvironment surrounding HRS cells frequently contains reactive B lymphocytes that express CD20, we hypothesized that targeting these reactive B cells by anti-CD20 RIT could deliver an effective radiation dose to HRS cells by a crossfire effect [7]. To test this hypothesis, patients with relapsed classical HL were treated with $^{90}$Y-ibritumomab tiuxetan (Zevalin) using an Institutional Review Board (IRB)-approved pilot clinical trial. Patients were considered eligible for the study if they had histologically confirmed, relapsed or refractory classical HL requiring treatment; relapsed from, refused, or were ineligible for stem-cell transplantation; and an absolute neutrophil count of $>$1500/$\mu$l and a platelet count of $>$100 000/$\mu$l. Patients who had prior autologous stem-cell transplantation were required to have backup stored stem cells of at least $2 \times 10^6$ CD34$^+$ cells/kg. Patients were excluded from the study if they had HL involving extranodal sites, including the bone marrow, nodular lymphocyte-predominant HL, prior allogeneic stem-cell transplantation, central nervous system lymphoma, pleural effusion, human immunodeficiency virus infection, total bilirubin $>$2.0 mg/dl, serum creatinine $>$2.0 mg/dl, or if they received prior external beam radiotherapy to $>$25% of bones. Four patients were treated on an IRB-approved study and all signed a consent form. Two patients received prior autologous stem-cell transplant. Biopsy materials from three cases were available for review and showed that CD20 was expressed by HRS cells in one case (Table 1). Reactive B cells comprised 5%, 10%, and 20% of the reactive cells surrounding HRS cells. All patients received 0.4 mCi/kg up to a maximum dose of 32 mCi. Favorable biodistribution of ibritumomab tiuxetan was confirmed in all four patients during the imaging phase. Tumor visualization was as follows: absent in one patient, faint visualization of some of the known lesions in two patients, and intense visualization of known disease sites in the supraclavicular, infraclavicular, mediastinal, hepatic, and abdominal lymphatic chains in one patient (Table 1). Following ibritumomab tiuxetan therapy, two patients had stable disease (less than a 50% reduction and less than a 25% increase in the sum of the products of two perpendicular diameters of all measured lesions and the appearance of no new lesions) and two had progression of disease. Treatment was well tolerated with hematologic toxicity similar to that observed in NHL patients treated with ibritumomab tiuxetan [8].

This is the first report using reactive B cells in the tumor microenvironment to indirectly deliver radiation to malignant HRS cells by crossfire effect. The theoretical advantages of this approach are (i) eliminate benign reactive B cells to deprive HRS cells from survival signals, (ii) directly kill CD20$^+$ HRS cells by RIT, and (iii) indirectly kill CD20$^-$ HRS cells by crossfire radiation from ibritumomab tiuxetan bound to normal infiltrating CD20$^+$ B cells. Although the number of patients in this report is small, our data indicate that this novel approach is feasible and safe. Tumor visualization was either absent or faint in three of the four patients, perhaps due to the small fraction of reactive B cells in the microenvironment (Table 1). A biopsy from the patient who had intense tumor imaging contained 20% reactive B cells. Future studies should examine whether there is a minimal requirement of reactive B cells in the microenvironment that is required for effective tumor imaging and to deliver a lethal dose to HRS cells. This will require carrying out needle biopsy and aspiration to quantify the percentage of CD20-expressing cells in HL lesions immediately before RIT and to correlate these findings with

### Table 1. Summary of patient characteristics, imaging, and treatment outcome

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age/sex</th>
<th>No. of prior treatment regimens</th>
<th>Prior stem-cell transplant</th>
<th>$^{90}$Y-ibritumomab tiuxetan dose (mCi/kg)</th>
<th>CD20 expression by HRS cells</th>
<th>% B cells in the microenvironment</th>
<th>Clinical response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25/male</td>
<td>3</td>
<td>Yes</td>
<td>None</td>
<td>0.4</td>
<td>−</td>
<td>5</td>
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<tr>
<td>2</td>
<td>74/male</td>
<td>1</td>
<td>No</td>
<td>Faint</td>
<td>0.4</td>
<td>+</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>31/female</td>
<td>5</td>
<td>Yes</td>
<td>Very faint</td>
<td>0.4</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>4</td>
<td>65/female</td>
<td>1</td>
<td>No</td>
<td>Intense</td>
<td>0.4</td>
<td>−</td>
<td>20</td>
</tr>
</tbody>
</table>

HRS, Hodgkin and Reed–Sternberg; PD, progression of disease; NC, no change.
tumor localization and treatment response. Furthermore, because the percentage of reactive B cells is relatively low, the need for pretreatment with cold anti-CD20 antibody should also be reexamined in this patient population.

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references


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