Prospective trial of targeted radioimmunotherapy with Y-90 ibritumomab tiuxetan (Zevalin) for front-line treatment of early-stage extranodal indolent ocular adnexal lymphoma

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Background: To determine the efficacy and side-effects of ⁹⁰Y ibritumomab tiuxetan (Zevalin) as front-line treatment in patients with early-stage extranodal indolent lymphoma of the ocular adnexa (orbit, conjunctiva, or eyelid).

Patients and methods: From August 2004 to November 2007, 12 patients with stages I–E extranodal indolent lymphoma of the ocular adnexa were enrolled in a prospective trial of rituximab followed by ⁹⁰Y ibritumomab tiuxetan (Zevalin therapeutic regimen). For each patient, clinical examinations and imaging studies were used to document response to therapy using the The International Working Group response criteria. All patients had ¹¹¹In ibritumomab tiuxetan imaging to confirm expected biodistribution before ⁹⁰Y-Zevalin therapy; in addition, three patients had an optional single photon emission computed tomography–computed tomography scan to estimate the absorbed radiation dose to the orbital and ocular tissues.

Results: The study included seven women and five men. The median age was 60 years (range 22–79). Nine patients had mucosa-associated lymphoid tissue lymphoma of conjunctiva or orbit; three patients had grades 1–2 follicular lymphoma of orbit. One patient who had been deemed stage I–E initially was found to have another lesion in her deltoid muscle on positron emission tomography 2 weeks after enrollment. She was kept on trial although her disease was reclassified as stage IV due to this single additional (biopsy-proven) site. Ten patients had a complete response and two partial response (PR) within 3 months of treatment. One patient had a recurrence in the upper eyelid 6 months after an initial PR; he then received 30 Gy of external-beam radiotherapy (EBRT). His disease later progressed again in the orbit and he is currently being considered for other treatments. A second patient who attained a PR has remained stable with no progression 12 months after treatment. With a median follow-up time of 20 months (range 6–44 months), there were no cases of distant (extraorbital) relapse. All 12 patients experienced grade I or II transient pancytopenia during the first 3 months after enrollment in the trial. There were no episodes of grade III or IV myelosuppression. The estimated absorbed radiation dose to the orbital soft tissues was <3 Gy, 10 times lower than that with EBRT.

Conclusions: Rituximab followed by ⁹⁰Y ibritumomab tiuxetan is an effective and safe front-line treatment for early-stage extranodal indolent B-cell lymphoma of the ocular adnexa.

Key words: orbital lymphoma, conjunctival lymphoma, radioimmunotherapy, Zevalin, ocular adnexal lymphoma, non-Hodgkin’s lymphoma

original article

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structures or a combination of these structures, is estimated to account for only ~2% of all cases of non-Hodgkin’s lymphoma (NHL) and about 5%–15% of all cases of NHL at extranodal sites [1–3]. Despite this, orbital lymphoma is the most frequent primary malignant tumor of the orbit in adults, accounting for ~55% of all orbital tumors [4]. A marked increase in the incidence of OAL has been observed in the last decade [5].
Mucosa-associated lymphoid tissue (MALT) lymphoma is the most common histologic subtype of OAL, followed by low-grade follicular lymphoma [6–8]. Diffuse large-cell lymphoma, mantle cell lymphoma, and other more aggressive histologic subtypes are less common in the ocular adnexal structures. Estimates of systemic (extraorbital) involvement associated with OAL range from 10% to 50% in most series [9–12]. The reported frequency of systemic involvement is a function of the histologic subtype and also depends on the systemic staging modalities used to detect extraorbital lymphoma [12, 13].

Various conventional treatment modalities have been used for OAL, including external-beam radiotherapy (EBRT), which is viewed as the gold standard for primary stages I–E extranodal lymphoma of the orbit [14, 15], single-agent or combination systemic chemotherapy regimens [16, 17], and combinations of radiotherapy and systemic chemotherapy.

In the last 10 years, targeted monoclonal antibody (mAb) therapy has become an important additional treatment modality for NHL [18–22]. Rituximab is the mAb most commonly used for treatment of lymphoma; it is a chimeric murine/human mAb directed against the cell-surface antigen CD20, which is expressed on all normal cells and at least 90% of NHL malignant B cells. Rituximab is approved for treatment of patients with relapsed or refractory low-grade or follicular B-cell NHL [19, 20]. The radioimmunoconjugate 90Y ibritumomab tiuxetan (Zevalin, Biogen IDEC, Cambridge, MA, succeed by Cell Therapeutics, Inc., Seattle, WA) is currently approved for treatment of patients with relapsed or refractory low-grade or follicular B-cell NHL, including patients with follicular NHL who are refractory to rituximab [23–26].

To our knowledge, the first published report of the use of mAbs (rituximab and 90Y ibritumomab) for treatment of OAL was our 2002 report on four patients with indolent lymphoma of the orbit treated at The University of Texas M. D. Anderson Cancer Center [27]. Three were treated with rituximab alone and one with rituximab followed by 90Y ibritumomab tiuxetan. The single patient treated with 90Y ibritumomab tiuxetan had complete response, defined as complete disappearance of all detectable clinical evidence of disease and disease-related symptoms and as of this writing has been free of disease for 7 years.

On the basis of our preliminary positive experience with 90Y ibritumomab tiuxetan for OAL [27], we designed a clinical trial of 90Y ibritumomab tiuxetan for front-line treatment of stages I–E indolent OAL. The rationale for this study was that systemic targeted radioimmunotherapy, if proven to be effective for OAL, might be associated with a lower rate of distant (extraorbital) relapse than EBRT or rituximab monotherapy and might be associated with less ocular toxicity than EBRT.

patients and methods

This was a prospective, single-arm, open-label study with The University of Texas M. D. Anderson Cancer Center as the only participating center. Appropriate institutional review board approval and an informed consent from each patient were obtained. During the informed consent process, each patient was told that radiotherapy is currently the gold standard treatment for early-stage extranodal indolent OAL.

The primary objective was to evaluate the efficacy of rituximab followed by 90Y ibritumomab tiuxetan as front-line treatment for early-stage indolent non-Hodgkin’s OAL. The secondary objectives were to establish the safety profile in this patient population and to estimate the absorbed radiation dose in the orbit using combined single photon emission computed tomography–computed tomography (SPECT/CT) in three patients who agreed to undergo this optional test.

eligibility criteria

Patients had to have biopsy-proven indolent follicular lymphoma or MALT lymphoma that predominantly involved the conjunctiva, orbit, or eyelid. They had to be ≥218 years old, have an expected survival of ≥3 months, have good performance status (Zubrod 0–2), and women had to be not pregnant or lactating. Pretreatment bone marrow biopsy was mandatory, and patients had to have acceptable hematologic status, including absolute neutrophil count ≥1500/mm³ and platelet count ≥100 000/mm³.

treatment and follow-up examinations

Each patient received rituximab, 250 mg/m² i.v., followed by an infusion of 111Indium, 5 ± 0.5 mCi, on the first day (for total-body imaging). Delayed whole body imaging was carried out 2 and 48 hours later to evaluate the biodistribution of Zevalin.. Approximately 1 week later, each patient received a second infusion of rituximab, 250 mg/m², followed by an infusion of 90Y ibritumomab tiuxetan. The dose was 0.3 mCi/kg for patients with a platelet count of 100 000/mm³–149 000/mm³ and 0.4 mCi/kg for patients with platelet count of >150 000/mm³. All patients had Indium imaging for total-body distribution. Patients were offered the opportunity to undergo quantitative radionuclide imaging (SPECT-CT) and dosimetry to estimate the radiation absorbed dose in the orbital and ocular tissues. The goal was to do orbital dosimetry using SPECT/CT in three patients who agreed to these optional procedures.

Each patient was evaluated with clinical examination and imaging studies including magnetic resonance imaging of the orbit and head and neck and computed tomography of the chest, abdomen, and pelvis every 3 months for the first 2 years and every 6 months thereafter for up to 4 years. Each patient had a complete blood count every week after study enrollment for 3 months and during each study visit thereafter.

response evaluation

Response to therapy was evaluated after 3 months on the basis of both clinical findings and radiographic findings. Standard response criteria were used to categorize responses on the basis of findings on radiographic imaging, clinical examination (including slit-lamp biomicroscopy and external examination of the conjunctiva and orbit), and, whenever possible, external photography [28].

If no response was seen 3 months after administration of 90Y ibritumomab tiuxetan (i.e. lack of decrease in size of tumor based on radiographic or clinical parameters), the patient was to exit the protocol and be evaluated for alternative standard forms of therapy, including EBRT or chemotherapy, as determined by the treating physician.

results

Patient and tumor characteristics and follow-up time are summarized in Table 1. There were seven women and five men between the ages of 22 and 79 years (median age 60 years). Nine patients had MALT lymphoma of the conjunctiva or orbit and three had grades 1–2 follicular lymphoma of the orbit. One patient was found to have a single lesion in her deltoid muscle on positron emission tomography 2 weeks after enrollment in the trial. Findings on subsequent magnetic resonance imaging of the same area were negative, but a biopsy confirmed a lymphoma focus in the deltoid muscle.
She was kept on the trial although her disease was reclassified as stage IV.

At the 3-month response assessment, two patients had a partial response (PR) (at least a 50% decrease in the size of the lesion) (Figure 1) and 10 had a CR (Figures 2 and 3). With a median follow-up time of 20 months (range 6–49 months), there were no cases of distant (extraorbital) relapse.

One patient (patient 7) had a recurrence in the upper eyelid 6 months after an initial PR (Figure 4). He exited the protocol and received EBRT (30 Gy). His disease later progressed again, and he is currently being considered for other treatment options. A second patient who achieved PR has not yet progressed after 12 months.

All 12 patients experienced grade I or II transient pancytopenia during the first 3 months after enrollment in the trial. Two patients had platelet transfusions, and one patient had blood transfusions due to myelosuppression (anemia). There were no episodes of grade III or IV toxicity. No patient experienced prolonged cytopenia beyond the first 12 weeks after treatment. Other side-effects were grades I–II fatigue (n = 8), increased bruising (n = 7), joint and muscle pain (n = 4), nausea (n = 3), headache (n = 3), fever (n = 1), dizziness (n = 1), and flushing (n = 1), all of which resolved after the first few weeks after treatment.

In all 12 patients, the distribution of isotope on 111In ibritumomab tiuxetan imaging was as expected, and there was no altered biodistribution. Three patients underwent a multiple SPECT/CT of the head and whole-body imaging at different intervals over 1-week period to estimate the radiation dose to the orbital and ocular structures. The estimated absorbed radiation dose to the orbital soft tissues was <3 Gy. The details of dosimetry for the orbit in these three

### Table 1. Patient and tumor characteristics

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, years</th>
<th>Race/ethnicity</th>
<th>Gender</th>
<th>Histologic subtype</th>
<th>Stage</th>
<th>Adnexal structure involved</th>
<th>Follow-up time, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>67</td>
<td>White</td>
<td>Male</td>
<td>MALT lymphoma</td>
<td>IE</td>
<td>Left conjunctiva</td>
<td>44</td>
</tr>
<tr>
<td>2</td>
<td>53</td>
<td>White</td>
<td>Female</td>
<td>MALT lymphoma</td>
<td>IVEa</td>
<td>Right lacrimal gland</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>White</td>
<td>Female</td>
<td>Follicular lymphoma, grade 1</td>
<td>IE</td>
<td>Left conjunctiva</td>
<td>36</td>
</tr>
<tr>
<td>4</td>
<td>59</td>
<td>White</td>
<td>Female</td>
<td>MALT lymphoma</td>
<td>IE</td>
<td>Right lacrimal gland</td>
<td>27</td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>White</td>
<td>Female</td>
<td>MALT lymphoma</td>
<td>IE</td>
<td>Right conjunctiva</td>
<td>27</td>
</tr>
<tr>
<td>6</td>
<td>67</td>
<td>Hispanic</td>
<td>Female</td>
<td>MALT lymphoma</td>
<td>IE</td>
<td>Left orbit</td>
<td>20</td>
</tr>
<tr>
<td>7</td>
<td>61</td>
<td>White</td>
<td>Male</td>
<td>Follicular lymphoma, grade 1 (predominantly) to grade 2 (focally), follicular and diffuse patterns</td>
<td>IE</td>
<td>Right upper eyelid</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>46</td>
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<td>Female</td>
<td>Follicular lymphoma, grade 1</td>
<td>IE</td>
<td>Left orbit</td>
<td>15</td>
</tr>
<tr>
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<td>Male</td>
<td>MALT lymphoma</td>
<td>IE</td>
<td>Left orbit</td>
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<tr>
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<td>IE</td>
<td>Left lacrimal gland</td>
<td>12</td>
</tr>
<tr>
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<td>Female</td>
<td>MALT lymphoma</td>
<td>IE</td>
<td>Right conjunctiva</td>
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</tr>
<tr>
<td>12</td>
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<td>White</td>
<td>Male</td>
<td>MALT lymphoma</td>
<td>IE</td>
<td>Right conjunctiva</td>
<td>6</td>
</tr>
</tbody>
</table>

*aThis patient’s disease was classified as stage IE on the basis of standard staging criteria; however, a total-body positron emission tomography scan identified a small lesion in the deltoid muscle that was confirmed on biopsy to represent a focus of lymphoma.

MALT, mucosa-associated lymphoid tissue.

### Figure 1. Magnetic resonance imaging of mucosa-associated lymphoid tissue lymphoma of the orbit in patient 9 before (A) and after (B) treatment with 90Y ibritumomab tiuxetan. There was significant (>50%) but partial resolution of the orbital mass. The residual mass has remained stable for 12 months after treatment.
patients are the subject of a separate paper which is currently under review.

**Discussion**

Our findings suggest that radioimmunotherapy with standard doses of $^{90}$Y ibritumomab tiuxetan is an effective and safe front-line treatment for early-stage extranodal indolent lymphoma of the ocular adnexa. The initial response rate was 100% with 83% complete responders. There were no cases of distant (extraorbital) relapse, with a median follow-up time of 20 months. These encouraging results suggest that radioimmunotherapy as front-line treatment for early-stage OAL may be similar to EBRT in terms of local control.

The most frequent side-effect associated with $^{90}$Y ibritumomab tiuxetan was grades I–II pancytopenia, which occurred during the first 3 months after treatment in every patient enrolled in the study. No patient experienced prolonged cytopenia beyond the first 12 weeks after treatment. Other side-effects included mild fatigue, nausea, and headache, all of which resolved after the first few weeks after treatment. The side-effects for patients in our trial are quite similar to those reported in previous trials of $^{90}$Y ibritumomab tiuxetan [29–31].

The estimated radiation dose to orbital and ocular tissues from treatment with $^{90}$Y ibritumomab tiuxetan was <3 Gy, about one-tenth the dose with EBRT. The details of estimation of radiation dose to the orbital and ocular soft tissues are the subject of another paper that is currently under review. We did not observe any ocular side-effects in patients treated in the trial. Specifically, there were no cases of cataract formation, dry-eye syndrome, or radiation retinopathy.

Radioimmunotherapy is appealing in lymphoma, which is considered to be inherently radiosensitive [32]. To our knowledge, the first published report of the use of mAbs (rituximab and $^{90}$Y ibritumomab tiuxetan) to treat OAL was our 2002 report in four patients with secondary indolent lymphoma of the orbit [27]. Three were treated with rituximab alone and one with rituximab followed by $^{90}$Y ibritumomab tiuxetan. All four patients had complete resolution of their...
orbital mass with a median follow-up time of 14.5 months, although two patients treated with rituximab monotherapy had distant relapse during the study period. The one patient treated with $^{90}$Y ibritumomab tiuxetan had a durable relapse-free response (7 years to date). Other case series describing treatment of OAL with rituximab alone have since followed. In 2004, Sullivan et al. reported eight patients in whom rituximab was used for treatment of OAL [33]. Only one of the eight patients had primary OAL and that patient also received radiotherapy, cyclophosphamide, vincristine, and prednisone. Two patients received rituximab alone; these patients experienced PR (one patient) or CR followed by recurrence (one patient). Zinzani et al. reported using rituximab as first-line therapy in a patient with a primary conjunctival lymphoma. The patient received four weekly i.v. infusions of rituximab. The lesion resolved after the fourth injection and completely disappeared 6 weeks after the start of therapy. There had been no recurrence at 5 months’ follow-up [34]. In another report, Ferreri et al. [35] reported that two patients with lacrimal gland lymphomas had a relapse at a median follow-up time of 5 months after the completion of primary rituximab therapy with one cycle of four weekly infusions. Rigacci et al. [36] treated nine patients with low-grade OAL (eight with MALT, one with follicular lymphoma) with a combination of rituximab and chlorambucil as first-line therapy. Eight patients (89%) had a complete remission and one a PR. At a median follow-up time of 25 months, all patients were alive; no instances of disease progression or late side-effects were observed. These investigators concluded that rituximab in combination with chlorambucil was feasible for first-line treatment of OALs [36]. In a report based on our own experience in all consecutive patients with OAL treated during a recent time period at our tertiary-care cancer center, we found that more than half of the patients were treated with rituximab in combination with various other treatment modalities [12]. This recent trend of using mAbs for treatment of OAL is a reflection of the overall trend in management of NHL [19, 21]. EBRT has been the most frequently used modality and is considered the gold standard for treating OAL because many patients with OAL present with localized disease [14, 15]. While EBRT remains a very effective form of local therapy for OAL, it does not address systemic sites of involvement of OAL in patients with multifocal disease and is associated with a risk of contralateral orbital relapse and systemic relapse [11]. Rates of systemic (extraorbital) involvement for OAL are estimated to range from 10% to 50% and are closer to 50% in series from tertiary cancer centers and in recent studies in which uniform staging including bone marrow biopsies and total-body positron emission tomography scans were used [6–12]. We believe that the risk of systemic involvement at initial diagnosis of OAL and the risk of future extraorbital relapse may be justifications for systemic therapy rather than EBRT for treatment of OAL. Furthermore, EBRT is associated with immediate and delayed ocular side-effects including dry-eye syndrome, ocular surface problems, cataracts, and, rarely, radiation retinopathy [37–39].

In conclusion, our preliminary results in this pilot trial suggest that $^{90}$Y ibritumomab tiuxetan may represent a reasonable alternative for front-line treatment of early-stage extranodal OAL, producing response rates similar to those with EBRT with one-tenth the absorbed radiation dose to orbital and ocular tissues. Continued monitoring of the patients in this trial is required to estimate the true relapse-free and progression-free survival rates. The results of this pilot trial may open the possibility of using...
radioimmunoconjugates as front-line therapy for early-stage indolent NHL at other sites.

references