First report on a prospective trial with yttrium-90-labeled ibritumomab tiuxetan (Zevalin) in primary CNS lymphoma

Sofiane Maza, Philipp Kiewe, Dieter L. Munz, Agnieszka Korfel, Bernd Hamm, Kristoph Jahnke, and Eckhard Thiel

Clinic for Nuclear Medicine (S.M., D.L.M.), Department of Hematology, Oncology, and Transfusion Medicine (P.K., A.K., K.J., E.T.), and Department of Radiology (B.H.), Charité-Universitätsmedizin Berlin, Berlin, Germany

Most patients with primary CNS lymphoma (PCNSL) relapse after primary therapy. Standard salvage treatment has not yet been established in PCNSL. Anti-CD20 immunotherapy has expanded treatment options in systemic B-cell lymphoma; however, its use is limited by reconstitution of the blood–brain barrier after tumor shrinkage. The aim of this phase II trial was to evaluate the therapeutic efficacy, toxicity, and biodistribution of yttrium-90 (90Y) ibritumomab tiuxetan in PCNSL. Ten patients with relapsed PCNSL were included in a phase II trial and treated with the 90Y-labeled anti-CD20 antibody ibritumomab tiuxetan. Nine patients actually received the planned radioimmunotherapy. In six patients, biodistribution of the antibody was measured by indium-111 (111In) ibritumomab tiuxetan whole-body scans and single-photon-emission CT (SPECT) of the brain. All patients were evaluated for toxicity and response at least 4 weeks after therapy. Four patients responded: one patient had a complete response lasting 30+ months, and three patients had short-lived responses of ≤4 weeks. Five patients progressed, and one patient did not receive treatment due to an infection prior to 90Y-antibody administration. Target accumulation of the antibody was demonstrated in four of the six patients examined by SPECT imaging with 111In ibritumomab tiuxetan. All patients experienced grade 3/4 hematotoxicity but no acute neurotoxicity. Penetration of a therapeutic antibody into PCNSL and significant clinical activity was shown. Because of limited response duration and considerable hematotoxicity, future investigations should focus on a multimodal approach with additional chemotherapy and preferably autologous stem cell support.

Keywords: 90Y ibritumomab tiuxetan, CNS lymphoma, imaging, PCNSL, Zevalin

Primary CNS lymphoma (PCNSL) is a rare type of usually aggressive B-cell non-Hodgkin’s lymphoma exclusively involving the CNS. Standard salvage therapy has not yet been established. Despite remission of PCNSL after primary therapy in the majority of patients, relapse occurs within 1–2 years in 30%-60% of patients, with a median survival after relapse of only 2–4 months.1

The anti-CD20 monoclonal antibody rituximab expanded treatment options in systemic B-cell lymphoma.2 The radiolabeled anti-CD20 antibody yttrium-90 (90Y) ibritumomab tiuxetan (Zevalin, Bayer Schering Pharma, Berlin, Germany) has demonstrated efficacy in systemic lymphomas even refractory to chemotherapy and rituximab, with only one treatment

Received August 7, 2008; accepted November 10, 2008.
S.M. and P.K. contributed equally to this work.
Address correspondence to Eckhard Thiel, Department of Hematology, Oncology, and Transfusion Medicine, Charité-Universitätsmedizin Berlin, Campus Benjamin Franklin, Hindenburgdamm 30/31, 12200 Berlin, Germany (Eckhard.Thiel@charite.de).

Copyright 2009 by the Society for Neuro-Oncology

Downloaded from https://academic.oup.com/neuro-oncology/article-abstract/11/4/423/1002275 by guest on 05 February 2019
course needed.\textsuperscript{3} Due to the large molecular size of 145 kDa, rituximab poorly penetrates the blood–brain barrier (BBB),\textsuperscript{4} which limits its use in PCNSL. According to PET, the BBB is initially leaky in PCNSL and reconstitutes after therapy-induced tumor shrinkage within 5 weeks.\textsuperscript{5} Therefore, a sufficient amount of \textsuperscript{90}Y ibritumomab tiuxetan (148 kDa) might be delivered to the tumor bulk in one treatment course.

The aim of this study was to evaluate the therapeutic efficacy, tumor penetration, and toxicity of \textsuperscript{90}Y ibritumomab tiuxetan in recurrent PCNSL.

**Patients and Methods**

**Study Design**

We planned to treat 10 patients with relapsed or refractory PCNSL in this phase II study. Primary end points were overall response and ibritumomab tiuxetan biodistribution; secondary end points were response duration, survival, and toxicity, including late neurotoxicity.

Inclusion criteria were histologically confirmed relapsed PCNSL after at least one prior treatment, age ≥ 18 years, KPS > 60, and human immunodeficiency virus (HIV) negativity. Exclusion criteria were evidence of systemic lymphoma, active infection, severe concomitant disease, inadequate cardiac, liver, and kidney function, and abnormal hematological parameters.

The study was approved by the local ethics committee, and informed consent was obtained from all patients.

**\textsuperscript{90}Y ibritumomab tiuxetan therapy**

An infusion of rituximab at 2.50 mg/m\textsuperscript{2} was given 8 days and 4 h before \textsuperscript{90}Y ibritumomab tiuxetan therapy to improve biodistribution of the radiolabeled antibody by binding to peripheral CD20\textsuperscript{+} B-cells. \textsuperscript{90}Y ibritumomab tiuxetan was given intravenously according to the standard regimen.

Seven patients were simultaneously treated with dexamethasone (2–8 mg three times daily) for 1 month. No concomitant antineoplastic therapy was given to the patients.

**Biodistribution and Tumor Uptake**

To evaluate antibody uptake in PCNSL after systemic intravenous administration, a dosimetric measurement study with ibritumomab tiuxetan labeled with the gamma emitter indium-111 (\textsuperscript{111}In) was performed in patients 1–6. These patients received 170–190 MBq of the gamma emitter after the first rituximab administration on day −8. On a SPECT/CT system (Hawkeye Millennium, GE Medical Systems, Slough, UK), whole-body scans and single-photon-emission CT (SPECT) were performed 1 h and 2–5 days thereafter. Regions of interest (ROIs) were drawn around the tumor regions that were localized by SPECT/CT performed on day −8 and/or pre-treatment brain MRI. The mean uptake values (counts/minute/pixel) were divided by the values determined in ROIs of the adjacent regions (background). The ratios were corrected for physical decay of \textsuperscript{111}In (see Fig. 2).

**Response Evaluation**

Response evaluation by contrast-enhanced MRI was scheduled before and 1 and 3 months after treatment as well as every 3 months thereafter in responders or if clinically indicated, according to the International PCNSL Collaborative Group criteria.\textsuperscript{6} Additional imaging by \textsuperscript{18}F-fluorodeoxyglucose-PET (FDG-PET) was performed in patient 9 before treatment and in patient 6 before and 1 month after treatment parallel to MRI.

**Results**

**Patient Characteristics**

Ten patients with median age of 53.5 years (range, 41–79 years) and median KPS scores of 80\% were included. Histology, obtained at first diagnosis, revealed diffuse large-cell B-cell lymphoma in all patients except patient 10, who had low-grade B-cell lymphoma. Patients received a median of three previous therapies (range, 1 to 7), including five patients that received previous whole-brain irradiation. Patient characteristics are given in Table 1.

Nine patients received the intended antibody treatment; patient 4, with concomitant diabetes and steroid treatment, was withdrawn due to pulmonary aspergillosis diagnosed after the first rituximab application and SPECT imaging but before treatment with \textsuperscript{90}Y ibritumomab tiuxetan.

**SPECT Imaging with \textsuperscript{111}In Ibritumomab Tiuxetan**

Imaging with \textsuperscript{111}In ibritumomab tiuxetan was performed in patients 1–6. Pretreatment MR images of these patients are shown in Fig. 1. SPECT revealed no lymphoma uptake in patients 1 and 6. Patients 3–5 showed prominent uptake in the tumors (Fig. 2). In patient 2, tumor uptake was assessable only by ROI evaluation (Fig. 3).

**Overall Response and Response Duration**

Four of the nine evaluable patients responded to \textsuperscript{90}Y ibritumomab tiuxetan treatment: Two patients showed complete response (CR) along with brief neurological improvement (patient 6 [see Fig. 4] and patient 7); one of them concomitantly received steroids. FDG-PET, performed before treatment and 4 weeks thereafter, in patient 6 showed decreased but still detectable FDG uptake. MRI, performed due to neurological deterioration, detected relapse with new lesions distant to the original target within 4 weeks in both patients. Uncertain complete remission on MRI with minimal residual contrast enhancement and neurological improvement after termination of steroid treatment was found in patient 10 and has been confirmed more than 30 months post-
Toxicity

All patients experienced hematotoxicity beginning 4 weeks after therapy. Grade 3/4 leukopenia was seen in seven of nine evaluable patients, and grade 3/4 thrombocytopenia in eight patients.

Patient 10 had grade 3 pneumonia during grade 3 leukopenia, and patient 1 died after pneumonia and sepsis with grade 4 leukopenia. Further toxicities included grade II stomatitis and thrombangitis obliterans in patient 2.
and pulmonary aspergillosis prior to treatment with $^{90}$Y ibritumomab tiuxetan in patient 4 (see Table 2).

**Discussion**

Imaging with $^{111}$In ibritumomab tiuxetan provided evidence that the antibody is able to cross the BBB at this stage of disease and accumulates within the target area 48 h and more after application. Furthermore, four of nine patients showed clinical responses to treatment with $^{90}$Y ibritumomab tiuxetan.

In a series of four patients with PCNSL, Dietlein et al.\(^7\) were not able to detect accumulation of iodine-123 ($^{123}$I)-labeled rituximab within the tumor on SPECT 1, 24, or 48 h after application. These time points were chosen based on quick in vivo dehalogenation of the compound and short physical half-life of $^{123}$I (13 h). In our study, however, we used a murine anti-CD20 antibody firmly conjugated to tiuxetan and $^{111}$In, which has a longer physical half-life (67 h). We postulate a delayed accumulation of the antibody in PCNSL in some patients due to remaining barrier function of the leaky BBB, demonstrated in patients 2 and 6 without assessable uptake (scan reading and uptake ratios) up to 6 days following administration but both showing at least PR. The clinical response in patients without uptake (especially in this small number of patients) is not surprising, because in larger imaging studies with other lymphomas a good correlation between nuclear medicine and clinical response could not always be shown. Iwamoto
et al. investigated \(^{111}\)In ibritumomab tiuxetan uptake in six PCNSL patients and found a 10-fold higher median dose of radiation in the lymphoma compared with normal brain tissue. Scans were acquired for up to 7 days following injection of \(^{111}\)In ibritumomab tiuxetan. The median clearance half-life within the lymphoma in this small patient cohort was calculated to be 96 h (range, 17–180 h), but no data were given regarding the time of maximum uptake.

We have not performed dosimetry in our patients. Doses reported by Iwamoto et al. ranged from 2 to 1,818 cGy (median, 701 cGy) within the lymphoma and only 17–130 cGy (median, 70 cGy) in normal brain tissue. With respect to neurotoxicity, we would not expect these doses to cause significant neurotoxicity even in patients pretreated with whole-brain irradiation. Sakamoto et al. reported on the use of stereotactic irradiation with concomitant chemotherapy in a small cohort.
of patients with PCNSL after prior whole-brain irradiation. They observed clinical activity in the absence of acute neurotoxicity. This is indicative of the radiosensitivity of PCNSL even in the recurrent situation.

The penetration of large molecules such as antibodies into the brain is limited to bulky tumor areas with at least partially disrupted BBB. Therefore, areas with small tumor cell accumulations with an intact BBB not visualized by MRI, as must be suspected in PCNSL, might not be reached by the antibody. This could explain why the observed responses were extremely short-lived, with new lesions occurring distant of the target tumor.

One approach to reach lymphoma cells beyond the BBB is to deliver treatment after prior osmotic BBB disruption by intra-arterial mannitol infusion. However, this approach requires adequate experience and careful patient selection. Doolittle et al. report on four patients receiving rituximab and chemotherapy after prior BBB disruption. To our knowledge, no treatment with ⁹⁰Y ibritumomab tiuxetan after BBB disruption has been reported thus far.

The toxicity observed was similar to that seen in other studies of ⁹⁰Y ibritumomab tiuxetan, with thrombocytopenia and leukopenia occurring approximately 4 weeks after therapy. Patients need to be closely monitored for hematological toxicity and infection. Importantly, no acute neurotoxicity was observed.

To date, experience with ⁹⁰Y ibritumomab tiuxetan in PCNSL is limited to a few case reports including combination treatment with temozolomide and a small study of six patients with recurrent PCNSL including imaging with ¹¹¹In ibritumomab tiuxetan.

The present study is the largest so far to investigate ⁹⁰Y ibritumomab tiuxetan treatment in PCNSL, demonstrating penetration into PCNSL along with significant clinical activity. In contrast to the study reported by Iwamoto et al., we saw complete disappearance of the tumor lesion in three of our patients. However, responses in our heavily pretreated patient cohort were short, and relapses occurred distant to target lesions. Moreover, we observed considerable delayed hematotoxicity causing infectious complications and interfering with salvage treatment. Despite the evidence of tumor penetration, monotherapy with ⁹⁰Y ibritumomab tiuxetan proved not to be sufficient for the treatment of recurrent PCNSL in our heavily pretreated patient cohort. Based on experiences with rituximab in high-grade lymphomas, combination of radioimmunotherapy with chemotherapy seems desirable. However, due to the observed hematotoxicity, such a multimodal approach would require autologous stem cell support.

Table 2. Treatment response, response duration, and toxicity grade referring to Common Terminology Criteria classification

<table>
<thead>
<tr>
<th>Patient</th>
<th>Response</th>
<th>Response Duration</th>
<th>Leukopenia</th>
<th>Thrombopenia</th>
<th>Nonhematological Toxicities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Unknown</td>
<td>NA</td>
<td>4</td>
<td>3</td>
<td>Death due to pneumonia and sepsis</td>
</tr>
<tr>
<td>2</td>
<td>PR</td>
<td>2 weeks</td>
<td>3</td>
<td>4</td>
<td>Thrombangitis obliterans, stomatitis</td>
</tr>
<tr>
<td>3</td>
<td>PD</td>
<td>NA</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>PD</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Pulmonary aspergillosis prior to ⁹⁰Y-ibritumomab tiuxetan</td>
</tr>
<tr>
<td>5</td>
<td>PD</td>
<td>NA</td>
<td>3</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>CR</td>
<td>4 weeks</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>CR</td>
<td>2 weeks</td>
<td>3</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>PD</td>
<td>NA</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>PD</td>
<td>NA</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>CRu</td>
<td>30+ months</td>
<td>3</td>
<td>1</td>
<td>Pneumonia (grade 3)</td>
</tr>
</tbody>
</table>

*After initial response evaluation.

Abbreviations: CTC, Common Terminology Criteria; NA, not assessed; PR, partial remission; PD, progressive disease; CR, complete response; CRu, uncertain complete remission.
References


