Phase II Trial of Short-Course CHOP-R Followed by $^{90}$Y-ibritumomab Tiuxetan and Extended Rituximab in Previously Untreated Follicular Lymphoma

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Abstract

Purpose: Radioimmunotherapy has been approved for relapsed follicular lymphoma (FL), including rituximab-refractory FL. This study was designed to determine the CR rate with short-course chemoimmunotherapy with cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab (CHOP-R) followed by $^{90}$-Y ibritumomab tiuxetan (RIT) with extended rituximab as first-line treatment.

Experimental Design: Between March 2004 and February 2007, 60 patients with stage II to IV symptomatic or bulky FL from a single institution supported by a large community network entered this phase II trial. Patients received CHOP-R for three treatment cycles before RIT followed by four additional weekly treatments with rituximab. Response was determined using fusion [${}^{18}$F] fluorodeoxyglucose-positron emission tomography (PET)-computed tomography (CT) imaging.

Results: Of the 60 patients entering this trial, 55 patients completed all protocol therapy. The median follow up was 19.7 months (range, 0.26-35.9 months). For intent-to-treat analysis, the complete response (CR) rate after CHOP-R, as assessed by CT and PET imaging, was 40% and 46%, respectively. After RIT, the CR rate improved, as assessed by CT and PET imaging, to 82% and 89%, respectively. Ten patients have progressed, including eight from best response of CR. Seven of 18 patients who were PET positive after CHOP-R progressed compared with 3 of 37 patients who were PET negative ($P = 0.010$).

Conclusions: In patients with previously untreated, symptomatic or bulky FL, short-course chemoimmunotherapy and consolidation RIT and extended rituximab resulted in a high CR rate. Failure to achieve an early PET CR after CHOP-R indicated high risk of relapse.

After three decades with little advance in the outcome for patients with follicular lymphoma (FL), the addition of the anti-CD20 chimeric monoclonal antibody, rituximab, dramatically changed the overall response rates (ORR) and may be affecting survival (1). As a single agent, rituximab was shown in a nonrandomized pivotal trial of 166 patients with relapsed low-grade lymphoma to have an ORR of 48% and a complete response (CR) of 6% (2). Lacking significant myelosuppression, investigators immediately recognized that rituximab was an ideal agent to combine with chemotherapy. Phase II studies combining chemotherapy with rituximab in relapsed and previously untreated patients with FL showed impressive ORR and CR rates of 90% to 100% and 50% to 70%, respectively (3, 4). Subsequently, two large randomized trials confirmed the benefit of combining chemotherapy with immunotherapy with CR rates of 41% and 20% compared with 10% and 17% with chemotherapy alone, significantly longer duration of response, and possibly, a survival advantage (5, 6).

Radioimmunotherapy is a promising new therapy demonstrating complete and partial responses in chemotherapy and rituximab refractory patients. As early as 1996, a phase II study using single agent 131-iodine (I) tositumomab (Bexxar; Glaxo-SmithKline), in previously untreated patients with FL, resulted in an ORR of 95% and a CR rate of 75% (7). In 2002, 90-yttrium(Y) ibritumomab tiuxetan (RIT; Zevalin; Biogen Idec) was approved by the Food and Drug Administration for the treatment of relapsed and refractory low-grade FL. RIT received approval based on ORR of 73% to 83% and CR rates of 15% to 51% depending upon the previous number and type of prior therapies (8, 9). Several small studies have reported

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CHOP-R Followed by RIT as First-Line Therapy in Follicular Lymphoma

Translational Relevance

The optimal treatment of advanced stage follicular lymphoma remains to be determined. With the addition of immunotherapy and radioimmunotherapy, the overall and complete response rates have improved. Furthermore, there is suggestive evidence that overall survival may be improved. In this study, we have sequenced a short-course of chemoimmunotherapy, cyclophosphamide, doxorubicin, vincristine, prednisone, and rituximab × 3 cycles, followed by radioimmunotherapy, 90-Y ibritumomab tiuxetan, and immunotherapy. Using fusion [18 F] 18F-fluorodeoxyglucose-positron emission tomography—computed tomography scans to determine response rate, a complete response was seen in 96% of patients who completed the therapeutic regimen. The progression-free survival and overall survival for patients completing all protocol therapy with a median follow-up of 19.7 months were 78% and 100%. Much longer follow-up will be necessary to determine the durability of these responses. This and additional studies will be necessary to define the appropriate place for radioimmunotherapy in the therapeutic algorithm for advanced follicular lymphoma.

Materials and Methods

Patients. This phase II, nonrandomized study, was carried out at a single institution supported by a large community oncology network. Radioimmunotherapy was administered at the central academic hub, the Hillman Cancer Center, but over half the patients received chemoimmunotherapy and follow-up at community offices. Between March 2004 through February 2007, 60 patients were enrolled. Eligibility criteria were as follows: FL grade of 1, 2, and 3 by WHO criteria; age of ≥18 y; no prior chemotherapy or monoclonal antibody therapy; prior radiation therapy was allowed if <25% of active bone marrow was exposed; Ann Arbor stages of II to IV with either symptomatic or bulky disease (>5 cm); performance status of 0 to 2; and measurable disease. A baseline MUGA scan within the institutional reference range was required. Patients with known HIV-related lymphoma were excluded. All patients signed a written informed consent approved by the University of Pittsburgh Institutional Review Board. Each patient received a FLIPI score based on age, stage, hemoglobin level, number of nodal sites of disease, and serum lactate dehydrogenase level and was classified as either asymptomatic, symptomatic, or with B symptoms. The largest cross-sectional diameter of a nodal mass was recorded as either <5 cm, from 5 to 10 cm, or >10 cm. A baseline PET-CT scan was recorded as either positive or negative for fluorodeoxyglucose uptake.

Drug administration. CHOP-R was administered at 21-d intervals. Rituximab 375 mg/m2 i.v was given on day 1 of each cycle. Standard Eastern Cooperative Oncology Group doses of CHOP were used (16). Doses were not modified, but use of growth factor and/or prophylactic antibiotics was allowed. For an absolute neutrophilic count of <1,500/mm3 or a platelet count of <100,000/mm3 on day 1 of subsequent cycles, chemotherapy was delayed 1 wk. A 2-wk delay was allowed for neutropenic fever. After three cycles of CHOP-R, patients were restaged with a PET-CT scan and bone marrow biopsy before receiving the RIT regimen. To proceed with RIT, bone marrow recovery was required as evidenced by an absolute neutrophilic count of ≥1,500/mm3, a platelet of ≥100,000/mm3, and bone marrow cellularity of ≥15%, and lymphoma infiltration of <25%. The details of RIT have been described elsewhere (17). Within 1 to 2 wk of receiving RIT, patients began an additional 4-wk course of rituximab 375 mg/m2 on days 1, 8, 15, and 22.

Clinical response criteria. Disease response and progression were determined by physical examination and fusion PET-CT scan done before therapy, 3 to 4 wk after 3 cycles of CHOP-R, at 12 wk post-RIT therapy to minimize posttherapy inflammatory changes (18, 19), and thereafter at 6-mo intervals. Bone marrow biopsy was done at baseline, after 3 cycles of CHOP-R, at 12 wk post-RIT therapy if either of the prior biopsies were positive. A CR included the following: resolution of all palpable peripheral adenopathy, a normocellular bone marrow without evidence of lymphomatous infiltration by histology or flow cytometry, the CT portion of the PET-CT scan meeting the international working group criteria, or the PET portion read visually as negative (18, 20). Partial response, stable disease, and progressive disease were determined by international working group criteria (20).

Assessment of molecular response. Quantitative PCR was done as described (21) using FAM-labeled forward primers directed toward BCL2 BCL2 mbr or mcr sequences and a reverse consensus primer for the IGH joining region. Copies of t(14;18)-positive DNA were calculated from standard curves of serially diluted plasmids containing inserts of either mbr or mcr BCL2/IgH joining region translocation regions from t(14;18)-positive patients. Because this aspect of the study required potentially serial bone marrows, participation was optional.

Toxicity. Adverse events were summarized for all patients who began any study therapy using the Common Toxicity Criteria of the National Cancer Institute version 3.0. All serious adverse events were discussed at a monthly disease center meeting. Serious adverse events that were either related, possibly or probably related to study treatment, but unexpected, were reported to the Institutional Review Board.

Statistical analysis. Follow-up time was computed using Kaplan-Meier with reverse censoring for deaths (22). We compared CR rates by disease characteristics with Fisher’s exact tests. Progression-free survival (PFS) was calculated as the time from the start of treatment to the date of lymphoma progression or death from any cause. Overall survival (OS) was computed as the time from the start of treatment to death from any cause. PFS and OS were computed based on all patients with follow-up information. Statistical analyses were done with S-Plus version 7.0 (Insightful Corp.).

Results

Patient characteristics. Sixty patients met eligibility criteria and are included in baseline characteristics, safety, and response calculations (Table 1). Five patients did not complete protocol therapy and follow-up (Fig. 1). The median age was 57 years (range, 27–78 years). The histologic or cytologic features included follicular grade 1 (28%), grade 2 (45%), and grade 3 (22%), and for 3 patients (5%), the grade was undetermined as the diagnosis was made on fine needle aspirate. The FLIPI risk groups included were as follows: low,
with 0 to 1 risk factors (25%); intermediate, with 2 risk factors (33%); and high, with 3 to 5 risk factors (42%). Bulky nodal disease was <5 cm in 30 patients (50%), 5 to 10 cm in 21 (35%), and >10 cm in 9 (15%). There were 30 (50%) asymptomatic patients, 12 (20%) with symptoms such as pain or excessive fatigue, and 18 (30%) with frank B symptoms. Bone marrow was considered positive if there was unequivocal involvement by histology and/or flow cytometry; equivocal or “suspicious” involvement was considered to be negative. Baseline bone marrow positivity was recorded as either <25% or >25% of the marrow space infiltrated with lymphoma. Thirty-five patients (58%) had positive bone marrow and 10 (17%) had >25% involvement. The baseline fluorodeoxyglucose PET scan was positive in 59 of 60 patients.

\[ \text{BCL2 gene translocation determination was measured in bone marrow specimens at baseline in 31 patients. Twelve of these 31 samples were tested at our institution, and 4 were positive. Twenty-eight of these samples were then sent to an outside laboratory and 6 were positive (US LABS).} \]

**Toxicity.** The expected CHOP-R related toxicities are shown in Table 2. Two patients died during the CHOP-R phase. One of these patients developed neutropenic sepsis during CHOP-R and presented to the hospital with hypotension and multisystem organ dysfunction. The other patient had a history of alcoholic cirrhosis and esophageal varices but was clinically compensated at the start of treatment. He had a lethal gastrointestinal bleed 48 hours after the start of chemotherapy. A third patient withdrew from the study after cycle 1 of CHOP-R because of decreased performance status, generalized weakness, and myopathy. One patient was removed from the study when a metastatic colon cancer was diagnosed after cycle 3 of CHOP-R. One patient was withdrawn from the study because of noncompliance. Grade 3 to 4 neutropenia occurred in 23 (39%) patients, and grade 3 to 4 thrombocytopenia occurred in 3 (5%) patients. There were a total of 3 (5%) hospitalizations due to neutropenic fever.

**Radioimmunotherapy-related toxicities.** The most frequent toxicity associated with RIT was myelosuppression (Table 2). Grade 3 to 4 neutropenia occurred in 28 (51%) patients. However, there was only one hospitalization for neutropenic fever. The incidence of grade 3 and 4 thrombocytopenia was 44%. One patient experienced a prolonged episode of serum sickness-like toxicity. This case has been described elsewhere (23).

**Second malignancies.** Three patients were diagnosed with second malignancies. One patient was diagnosed with metastatic colon cancer on the PET-CT imaging study done after cycle 3 of CHOP-R. Another patient developed a PET-positive pelvic mass, which was diagnosed as an endometrial cancer 11 months after completing therapy. A third patient was found on routine mammography, 9 months after protocol therapy, to have an early stage breast cancer. In retrospect, two of the malignancies were likely present at the time of the diagnosis of FL. The finding of a solid tumor malignancy is not unexpected in this age group in the general population (24). There has not been any case of MDS or acute myelogenous leukemia observed in our patients.

**Clinical outcomes.** Of the 60 patients entering this trial, 56 were evaluable for response after 3 cycles of CHOP-R (Fig. 1). There were 55 patients who completed all protocol therapy. According to intent-to-treat analysis of 60 patients consented, the CR rate after CHOP-R as determined by CT and PET imaging was 40% and 44%, and increased to 82% and 89% after RIT and extended rituximab, respectively. For the 55 patients who completed both CHOP-R and RIT and extended rituximab, the CR rate was 44% (CT) and 67% (PET), and increased to 89% (CT) and 96% (PET), respectively. In specific

### Table 1. Clinical characteristics of 60 patients enrolled on study

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>&lt;60 39 (65%)</th>
<th>≥60 21 (35%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male 32 (53%)</td>
<td>Female 28 (47%)</td>
</tr>
<tr>
<td>Histologic grade</td>
<td>1 17 (28%)</td>
<td>2 27 (45%)</td>
</tr>
<tr>
<td>FLIPI risk</td>
<td>Low 15 (25%)</td>
<td>Intermediate 20 (33%)</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Negative 25 (42%)</td>
<td>Positive 35 (58%)</td>
</tr>
<tr>
<td>Bulk lesion</td>
<td>&lt;5 cm 30 (50%)</td>
<td>5-10 cm 21 (35%)</td>
</tr>
</tbody>
</table>

**Assessed for eligibility (n=61)**
- Excluded - Not meeting eligibility criteria (n=1)
- CHOP-R Therapy (n=60)
- Discontinued CHOP-R Non-compliant (n=1) Septic death (n=1) G1 bleed (n=1) Neuropt (n=1)
- PET neg (n=37) PET pos (n=19)
- RIT Therapy (n=18) Colon ca diagnosis (n=1)
- PET neg (n=16) PET pos (n=2)
- Progressed (n=3, 8%) Progess (n=6, 31%) Progess (n=2, 100%)
regard to the PET responses in the 55 patients who completed both phases of the study, after CHOP-R, 37 (67%) patients were PET negative and 18 (33%) were PET positive. After RIT, another 16 patients became PET-negative for a total PET CR rate of 96%. PET CR rate by stage, FLIPI score, bulk disease, histologic grade, and bone marrow status is shown in Table 3.

The mean estimated follow-up for all 60 patients was 19 months (median, 19.7-35.9 months). Ten patients progressed (eight whose best response was CR, one from partial response, and one from stable disease). Among these 10 patients who progressed (Table 4), 7 were PET positive after CHOP-R. Two patients did not achieve PET-negative status after RIT and progressed within 6 months. Seven of the 18 patients who remained PET-positive after three cycles of CHOP-R and who then received RIT progressed, compared with only 3 of 37 patients who were PET negative after CHOP-R ($P = 0.010$). All of the progressed patients had stage IV disease with bone marrow involvement. Four patients who progressed had >25% marrow involvement at baseline. Biopsy material was available for 8 of the 10 patients at the time of relapse. One patient had transformation to a diffuse large B-cell lymphoma, whereas the others continued to have a follicular pattern. On an intent-to-treat basis, the PFS and OS at 24 months were 73% and 94.8%, respectively. The PFS and OS for patients completing all protocol therapy at 24 months were 78.4% and 100% (Fig. 2A and B).

### Discussion

This study was designed based on the favorable experience using I-131 tositumomab as a single agent in previously untreated patients with FL (7). In that study, the ability to achieve a CR was significantly decreased in patients with a maximal nodal mass of >5 cm and bone marrow involvement.

### Table 3. CR rate by patient characteristic

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n = 60 (intent to treat, all patients)</th>
<th>n = 55 (patients who completed study protocol and RIT)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CR by PET</td>
<td>Statistical significance</td>
</tr>
<tr>
<td></td>
<td>Number</td>
<td>%</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>6/6</td>
<td>100%</td>
</tr>
<tr>
<td>III</td>
<td>19/21</td>
<td>90%</td>
</tr>
<tr>
<td>IV</td>
<td>28/33</td>
<td>85%</td>
</tr>
<tr>
<td>FLIPI Low</td>
<td>15/15</td>
<td>100%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>18/19</td>
<td>95%</td>
</tr>
<tr>
<td>High</td>
<td>20/26</td>
<td>77%</td>
</tr>
<tr>
<td>Bulk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;5 cm</td>
<td>29/30</td>
<td>97%</td>
</tr>
<tr>
<td>5-10 cm</td>
<td>19/22</td>
<td>86%</td>
</tr>
<tr>
<td>&gt;10 cm</td>
<td>5/8</td>
<td>63%</td>
</tr>
<tr>
<td>Grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>16/17</td>
<td>94%</td>
</tr>
<tr>
<td>2</td>
<td>23/27</td>
<td>85%</td>
</tr>
<tr>
<td>3</td>
<td>11/13</td>
<td>85%</td>
</tr>
<tr>
<td>Undetermined</td>
<td>3/3</td>
<td>100%</td>
</tr>
<tr>
<td>BM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>23/25</td>
<td>92%</td>
</tr>
<tr>
<td>Positive</td>
<td>30/35</td>
<td>86%</td>
</tr>
</tbody>
</table>

All $P$ values from Fisher's exact test.
For all patients, PFS at a median follow-up of nearly 8 years was 50%; however, for partial responders, median PFS was 1 year, and for complete responders, which includes 75% of patients, median PFS has not been reached at 8 years (25). Therefore, this suggested that in the subset of patients who did not achieve a CR, radioimmunotherapy alone might be insufficient to achieve long-term remissions. The design of our study was to take advantage of the expected synergy of combining a short-course of chemoimmunotherapy as a debulking therapy, followed by consolidation of the remission with RIT and extended rituximab, thus decreasing the duration of therapy and possibly decreasing the potential long-term toxicities of chemotherapy. Although the rationale for extended rituximab was based on the superior event-free survival in chemotherapy-naive patients treated with eight doses of rituximab compared with the standard four doses without chemotherapy (26), the extended rituximab does potentially confound the precise contribution of RIT. Our study included patients with high-risk characteristics, including grade 3 histology (22%), intermediate and high FLIPI risk (75%), bulky disease of ≥5 cm (50%), B symptoms (30%), and baseline bone marrow involvement of >25% (17%). Nonetheless, this regimen resulted in a CR rate by PET imaging of 96% in those patients completing protocol therapy.

Since the publication of the international working group criteria for response assessment of lymphoma (20), CT has been the predominant imaging study for judging response rate. Shortcomings of determining a CR by CT are well-known, including relatively minor differences in the measurement of the size of a node and the inability to determine if residual enlarged nodes by size criteria contain viable lymphoma. PET has gained widespread use as a functional imaging tool for staging and response assessment in lymphomas (27–29). Correlation with response by PET and outcome has been suggested for diffuse large B-cell lymphoma and Hodgkin lymphoma but remains less well-established for other histologies. In aggressive lymphoma and Hodgkin lymphoma, the failure to achieve early fluorodeoxyglucose-PET negativity after two to three cycles of combination chemotherapy was predictive of relapse, even if imaging studies became negative after completion of a full course of chemotherapy (30–32). In our study, patients who remained PET-positive after three cycles of CHOP-R were significantly more likely to progress. The potential for early prediction of failure has not been previously reported for FL.

Table 4. Characteristics of progressed patients

<table>
<thead>
<tr>
<th>Relapsed Pt #</th>
<th>Age</th>
<th>Bone marrow</th>
<th>Stage</th>
<th>Grade</th>
<th>FLIPI risk</th>
<th>PET post-CHOP</th>
<th>PET post-RIT</th>
<th>Bulk (cm)</th>
<th>Relapse biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>46</td>
<td>+</td>
<td>IV</td>
<td>2</td>
<td>2</td>
<td>Pos</td>
<td>Neg</td>
<td>3.4</td>
<td>Follicular</td>
</tr>
<tr>
<td>6</td>
<td>70</td>
<td>+</td>
<td>IV</td>
<td>2</td>
<td>3</td>
<td>Pos</td>
<td>Neg</td>
<td>5.8</td>
<td>Follicular</td>
</tr>
<tr>
<td>9</td>
<td>59</td>
<td>+</td>
<td>IV</td>
<td>3</td>
<td>2</td>
<td>Pos</td>
<td>Neg</td>
<td>14</td>
<td>Follicular</td>
</tr>
<tr>
<td>13</td>
<td>42</td>
<td>+</td>
<td>IV</td>
<td>3</td>
<td>3</td>
<td>Pos</td>
<td>Pos</td>
<td>13.5</td>
<td>Follicular</td>
</tr>
<tr>
<td>16</td>
<td>61</td>
<td>+</td>
<td>IV</td>
<td>1</td>
<td>3</td>
<td>Neg</td>
<td>Neg</td>
<td>4.8</td>
<td>N/A</td>
</tr>
<tr>
<td>17</td>
<td>62</td>
<td>+</td>
<td>IV</td>
<td>1</td>
<td>3</td>
<td>Neg</td>
<td>Neg</td>
<td>6</td>
<td>Follicular</td>
</tr>
<tr>
<td>33</td>
<td>60</td>
<td>+</td>
<td>IV</td>
<td>Undetermined</td>
<td>3</td>
<td>Neg</td>
<td>Neg</td>
<td>4.2</td>
<td>N/A</td>
</tr>
<tr>
<td>45</td>
<td>51</td>
<td>+</td>
<td>IV</td>
<td>2</td>
<td>4</td>
<td>Pos</td>
<td>Pos</td>
<td>7.4</td>
<td>Large cell</td>
</tr>
<tr>
<td>48</td>
<td>51</td>
<td>+</td>
<td>IV</td>
<td>1</td>
<td>2</td>
<td>Pos</td>
<td>Neg</td>
<td>7</td>
<td>Follicular</td>
</tr>
<tr>
<td>53</td>
<td>66</td>
<td>+</td>
<td>IV</td>
<td>2</td>
<td>3</td>
<td>Pos</td>
<td>Neg</td>
<td>3.8</td>
<td>Follicular</td>
</tr>
</tbody>
</table>

Abbreviations: Pos, positive; neg, negative; N/A, not available.

Fig. 2. Kaplan-Meier analysis for PFS and OS. A, PFS shown for all consented patients, all patients who received RIT, PET-positive after CHOP-R, and PET negative after CHOP-R. B, OS shown for all consented patients, all patients who received RIT, and 95% confidence interval for all consented patients.
Transformation of FL to diffuse large B-cell lymphoma occurs in approximately one-third of patients diagnosed with FL. Some investigators prefer to keep anthracyclines in reserve should transformation occur. However, in a study using anthracycline-based chemotherapy upfront, it seemed that aggressive initial therapy might actually decrease the incidence of transformation (33). In our study, only one relapsed patient was documented to have transformed to diffuse large-cell histology.

The major toxicity associated with RIT was myelosuppression. Both grade 4 neutropenia and thrombocytopenia occurred in 20% of patients. There was only one episode of febrile neutropenia after RIT. In comparison to post-CHOP treatment with 131I tositumomab (10), myelosuppression seems to be slightly greater with RIT. Although it is most likely attributable to RIT, rituximab may have contributed. However, all 55 patients who received RIT had normal white blood counts and platelet counts by week 12 post-RIT.

In our design of this study, we hypothesized that we would be able to measure an increased depth of complete remission by adding PET scanning and molecular assessment of response to the standard use of CT imaging. Of the 31 patients who had bone marrow samples available for baseline testing for the BCL2 gene rearrangement, only 9 were positive and thus precluded a formal analysis. This is a much lower rate of BCL2 positivity than generally reported in the literature (34). These results point out the need for a reproducible, standardized, and universally accepted assay before BCL2 gene rearrangement can be prospectively evaluated and compared with PET imaging for measurement of response and as a predictor of durability of response.

A number of studies have shown that chemoimmunotherapy results in a higher CR rate than chemotherapy alone. In one large randomized trial, the CR rate for R-CVP was 41% (5,24) and in another trial, the rate for CHOP-R was 20% (6).

Although these CR rates are much lower than phase II studies of chemoimmunotherapy and in studies incorporating chemoinmunotherapy followed by first-line radioimmunotherapy, the wide range of CR rates serves to emphasize the importance of patient selection and study design, and thereby underscores the need for large randomized studies before a paradigm shift in therapy can occur. A pivotal study is being conducted by the intergroup mechanism, comparing six cycles of CHOP-R with six cycles of CHOP followed by 131I tositumomab. This study may establish the role of upfront radioimmunotherapy; however, the superiority of CHOP-R over CHOP alone may limit the benefit of radioimmunotherapy in this trial. Although there is a theoretical concern that rituximab may block potential binding sites for radio-labeled monoclonal antibodies, we saw a significant number of patients (29%) convert from partial responders after CHOP-R to complete responders after RIT, suggesting that RIT was not blocked by rituximab. Additional randomized studies comparing the optimal chemoimmunotherapy regimen with sequential chemoimmunotherapy and RIT may be needed.

PET positivity after three cycles of CHOP-R seems to be an indicator of more resistant disease and predictive of relapse. This suggests intrinsic differences between patients who achieve early response and those with more resistant disease. Studies in lymphoma cell lines have shown that there are differences in cell signaling pathways that predict sensitivity and resistance to both chemotherapy and rituximab. Analysis of these pathways in patient tissues may be the next critical step in understanding and optimizing targeted therapy (35,36).

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

### References


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