Phase II study of rituximab plus ABVD in patients with newly diagnosed classical Hodgkin lymphoma

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ABSTRACT

We evaluated the efficacy and safety of rituximab in combination with standard doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) in patients with classical Hodgkin lymphoma (cHL). In this phase II study, patients with chemotherapy naive advanced stage cHL were treated with rituximab 375 mg/m² weekly for six weeks and standard ABVD for six cycles. The primary outcome is event free survival (EFS) at five years. 85 patients were enrolled, of whom 78 patients were eligible. With a median follow up duration of 68 months (range 26-110), and based on an intent-to-treat analysis, the five-year EFS and overall survival (OS) rates were 83% and 96%, respectively. The five-year EFS for patients with stage III/IV was 82%. Furthermore, the five-year EFS for patients with International Prognostic Score (IPS) of 0 to 2 was 88% and for those with IPS score of > 2 was 73%. The most frequent treatment-related grade 3 or 4 adverse events were neutropenia (23%), fatigue (9%), and nausea (8%). Our results demonstrate that the addition of rituximab to ABVD is safe and has a promising clinical activity in patients with advanced stage cHL. This data is currently being confirmed in a multicenter randomized trial. This trial has been completed and is registered with www.ClinicalTrials.gov, number NCT00504504.
INTRODUCTION

The majority of patients with newly diagnosed classical Hodgkin lymphoma (cHL) are cured with initial multi-agent chemotherapy. Among multiple chemotherapy regimens, ABVD and BEACOPP remain the most widely used regimen for the treatment of patients with advanced stage cHL. Because undesired short-term and long-term treatment-related toxicity continues to be problematic for this relatively young patients population, the development of more safe and effective front-line regimens continues to be actively pursued.

The anti-CD20 monoclonal antibody rituximab has demonstrated a good safety profile and clinical activity in a wide variety of B-cell lymphomas, all of which express CD20 antigen on the malignant B-cells. Subsequent studies that combined rituximab with front-line chemotherapy regimens resulted in improvement in the EFS, and in several cases in the overall survival of different non-Hodgkin lymphoma subtypes. In Hodgkin lymphoma, the malignant cells express CD20 in all cases of lymphocyte predominant subtype, but only in 20%-30% of the cHL subtype. In those cases, rituximab also demonstrated single agent activity. Emerging data suggested that rituximab may also have a therapeutic value in patients with cHL whose tumors do not express CD20, by either depleting reactive B lymphocytes from the microenvironment which may enhance anti-tumor immunity, and/or by killing the putative CD20-expressing HL stem cells. With this background, we conducted a phase II study to evaluate the safety and efficacy of rituximab in combination with standard ABVD chemotherapy in patients with advanced stage cHL.

PATIENTS AND METHODS

Patients

This is a single institution open label, non-randomised, phase II study. Eligible patients were required to have histologically confirmed chemotherapy naive advanced stage cHL (stage II bulky, III or IV disease), or relapsed cHL after radiation therapy alone. Patients were required to be >16 years of age; have bidimensionally measurable disease ≥ 2.0 cm; have absolute neutrophil count (ANC) ≥ 1000/mm$^3$, platelet count ≥ 100x10$^3$ /mm$^3$, serum creatinine 176.8 µM (2 mg/dL) or less, serum bilirubin 34.3 µM (1.5 mg/dL) or less and left
ventricular ejection function \textgeq 50\% on nuclear cardiac scan or echocardiogram. Patients were excluded if they were pregnant; had HIV infection, active hepatitis B or C infection, or severe pulmonary disease. All patients provided written, informed consent in accordance with the Declaration of Helsinki. The study was approved by an institutional review board at all sites. This trial has been completed and is registered with ClinicalTrials.gov, number NCT00504504.

**Treatment**

Rituximab was given at 375 mg/m\(^2\) intravenously weekly for six weeks, with the first dose given on the same day of the first dose of ABVD (doxorubicin 25 mg/m\(^2\), bleomycin 10 units/m\(^2\), vinblastine 6 mg/m\(^2\), and dacarbazine 375 mg/m\(^2\)). ABVD was given on days one and 15 of 28-day cycle for six cycles. The use of growth factor support and consolidation radiation therapy was allowed at the treating physicians’ discretion.

**Assessment of response and toxicity**

The primary objective of the study was to evaluate the five-year event free survival rate (EFS). The secondary objectives were to assess toxicity and response rates including complete response (CR), CR unconfirmed (CRu), and partial response (PR) and five-year overall survival (OS). Response was determined according to International Working Group (IWG) criteria reported in 1999, based on CT scan, bone marrow biopsy results.\textsuperscript{20} Assessments were performed during therapy after two to three cycles of ABVD, and after completing the planned six cycles of ABVD. Subsequently, patients were evaluated every three to four months during years one and two, and every six months during years three to five. After five years, in the absence of new symptoms, patients were evaluated on a yearly basis. PET scan was not required, as the trial was initiated before PET scan was introduced to practice. At treating physicians’ discretion, PET scan could be performed before, during and at the end of therapy. The PET scan results were reported in real-time by M. D. Anderson clinical nuclear medicine radiologists, using visual assessment based on the criteria published by Juweid et al.\textsuperscript{21} Briefly, mediastinal blood pool activity was used as the reference background activity to define PET positivity for a residual mass \textgeq 2 cm in greatest transverse diameter, regardless of its location. A smaller
residual mass or a normal sized lymph node (i.e., $\leq 1 \times 1$ cm in diameter) was considered positive if its activity was above that of the surrounding background. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria version 3.

**Statistical analysis**

EFS was defined as the time from the study entry to disease progression, relapse or death from any cause. OS was calculated from the study entry to death of any cause. Kaplan-Meier plots were used to depict the PFS and OS, and difference in the survival in two groups was compared by log-rank test using GraphPad Prism Version 5 (La Jolla, CA). Efficacy analyses were performed on an intent-to-treat basis. The success of the study was to be evaluated in terms of the five-year EFS rate. We originally intended to compare the five-year EFS rate in this study to that in a large previous study including 115 patients treated with ABVD, which was 61% \(^1\). We planned to enroll 70 patients over 4 years based on an expected accrual rate of 1.5 patients per month. With this number of patients, assuming exponentially distributed EFS times, estimated five-year EFS rate of 74% was to be declared significantly superior given 3 additional years of follow up after the end of accrual (one-sided significance level of 0.05 and power of 80%). As the five-year EFS rate was not a reasonable parameter to formulate early stopping rule, we used a response rate instead. An early stopping rule was implemented to ensure that the response rate is not lower than expected 95% \(^1\). Therefore, at least 12 of the first 14 patients (90% confidence interval of response rate is 65-95%) were required to achieve CR, CRu or PR before further patients could be enrolled.

When analyzing data after completing planned enrollment (March 2001 to March 2005, N=70), we identified only 20 patients with poor risk features (International Prognostic Score (IPS) > 2) who had an estimated 3-year EFS of 73%. This favorable outcome prompted us to seek an IRB approval to enroll an additional 15 patients with IPS score of > 2 to further examine the activity of RABVD in patients with poor risk features (enrolled between March 2005 and August 2007).
RESULTS

Patients

85 patients were registered on this study between March 2001 and August 2007 (Figure 1). Seven patients were found ineligible after registration (one with diffuse large B-cell lymphoma, one with nodular lymphocyte predominant Hodgkin lymphoma and five with stage IA or stage IIA non-bulky disease). Thus, 78 eligible patients received at least one dose of RABVD and were evaluable for treatment toxicity and efficacy. Characteristics of these 78 patients are summarized in Table 1. Five patients had poor compliance with the treatment and response assessment schedules, which precluded documentation of end of therapy response assessment. Thus, a total of 73 patients were evaluated for objective response. All 78 patients, including the 5 non-compliant patients, were evaluated for EFS and OS based on intent-to-treat analysis.

Response to therapy

Since the trial was initiated before PET scan was introduced to practice, the response evaluation in this trial is based on CT scan according to IWG criteria reported in 1999. CR, and Cru were achieved in 49 and 19, patients (93%), respectively, and 4 achieved partial remissions. One patient experienced progressive disease after three cycles of RABVD and received salvage chemotherapy.

The median follow up duration of surviving patients is 68 months (range 26-110 months). Based on an intent-to-treat analysis, the five-year EFS and OS rates were 83% (95% confidence interval (CI) 72% - 90%) and 96% (95% CI 88%-99%), respectively (Figure 2A). EFS was then analyzed by Ann Arbor stage, IPS, and the expression of CD20 on Hodgkin and Reed-Sternberg (HRS) cells. The five-year EFS in patients with stage II and stage III/IV were 82% and 82% (Figure 2B). The five-year EFS rates in patients with IPS of 0 to 2 (n=43) and those with IPS of > 2 (n=35) were 88% (95% CI; 74% - 95%) and 73% (95% CI; 50% - 86%), respectively (p=0.127, Figure 2C).
CD20 expression on HRS cells was evaluated in 70 patients; 14 (20%) expressed CD20 and 56 (80%) did not. The five-year EFS in patients with CD20 positive tumors was 93% compared with 77% for those with CD20 negative tumors (p=0.230, Figure 3A).

Interim PET scan results have been shown to predict long term outcome of ABVD therapy in patients with cHL. We investigated whether interim PET status maintains its predictive prognostic value in patients treated with RABVD. For this analysis, we used real-time prospective interim PET results, which were performed after two or three cycles of RABVD, and were interpreted by M. D. Anderson clinical diagnostic nuclear medicine radiologists. Interim PET scan was performed in a total of 65 patients. The five-year EFS rates in patients with interim PET negative (n=52) and those with interim PET positive (n=13) were 91% and 77%, respectively (p=0.076, Figure 3B).

Toxicity

All 78 eligible patients received at least one dose of RABVD and were evaluated for toxicity. All patients received pre-treatment anti-emetics, and were allowed to receive growth factors prophylaxis. Seventy-six patients received six weekly doses of rituximab as scheduled, and 2 did not due to poor compliance. One patient experienced prolonged cytopenia after five cycles of RABVD and did not receive the sixth cycle. One patient developed Pneumocystis pneumonia following third cycle that resolved with proper therapy. The most frequent treatment-related grade three and four adverse events were neutropenia in 18 patients (23%), fatigue in seven patients (9%), and nausea in six patients (8%).

Discussion

Over the past decade, the addition of anti-CD20 naked antibody rituximab to standard frontline chemotherapy regimens have improved treatment outcome, including survival, of patients with B-cell non-Hodgkin lymphoma. Because HRS cells rarely express CD20, and they uniformly express CD30, previous efforts focused on the development of monoclonal antibodies targeting CD30. Unfortunately, several naked anti-CD30 antibodies
failed to produce meaningful clinical responses precluding further clinical development. In this report, we demonstrate that targeting CD20 in combination with ABVD is safe and has promising clinical activity for the treatment of patients with advanced stage cHL. Though this is a single arm open label study, our results compares favorably to those recently reported with ABVD alone in similar patient population, especially those who were treated around the same period of time at our institution and elsewhere (supplemental Figure 1).4,6,24 More recently, Kasamon et al conducted a phase-II multicenter study of RABVD in a similar patient population, and independently confirmed our results, as they reported with a 3-year EFS rate of 83% in 49 patients.25 Given these encouraging results, we have initiated a multicenter randomized study comparing standard ABVD with RABVD in patients with advanced stage cHL with IPS>2. (Clinicaltrials.gov NCT00654732)

In Hodgkin lymphoma, CD20 expression on the malignant cells is detected in all nodular lymphocyte predominant cases, and in up to 30% of cHL. In these cases, single agent rituximab produced high response rates.17,26 In a pilot study, rituximab demonstrated efficacy in patients with relapsed cHL, regardless of CD20 expression by HRS cells.27 Twenty-two patients with relapsed classical HL were treated with six weekly doses of rituximab. Five (22%) patients achieved partial or complete remissions, and eight additional patients had stable disease. Clinical remissions were observed in patients regardless of CD20 expression by HRS cells, but response were limited to patients whose disease was confined to lymph nodes.27 In this study, patients with CD20+ HRS cells tended to have a better EFS compared to those whose HRS cells did not express CD20 (93% vs. 77%), although this difference was not statistically significant. The benefit of rituximab in patients with CD20-negative tumors might be explained by eliminating reactive B-cells in the microenvironment that may support the growth and survival of HRS cells.28 Eliminating reactive B-cells may also enhance the anti lymphoma immune response.18 A third potential mechanism is targeting the putative HRS stem cells which are reported to express CD20.19

Patients with poor risk features are considered candidates for investigational therapy. The two most widely used prognostic factors are the IPS score and interim PET scan results.23,29 In our study, patients with IPS >2 had a 5-year EFS of 73%, which is better than expected when ABVD alone was used. In this study, patients with negative interim PET imaging results had a better 5-year EFS compared to those with positive
interim PET results (91% vs. 77%). Thus, our data confirms the prognostic value of interim PET in patients receiving RABVD. However, patients who had positive interim PET had a far better outcome compared with what has been previously reported with ABVD alone.23 The different outcome between these two studies may be related to the retrospective nature of the ABVD study, but may also suggest that the addition of rituximab to ABVD may improve treatment outcome especially in patients with positive interim PET results. These encouraging results provided a rationale for an ongoing multicenter randomized clinical trial comparing RABVD to standard ABVD in patients with high-risk advanced stage cHL (clinicaltrials.gov NCT00654732). In a different strategy, the German Hodgkin Lymphoma Study Group is currently investigating the role of rituximab in combination with BEACOPP in patients with positive interim PET scan (clinicaltrials.gov NCT00515554).

Since the initiation of our study, the antibody drug conjugate brentuximab vedotin was recently demonstrated a remarkable single agent activity in patients with relapsed cHL, resulting in its approval by the U.S. Food and Drug Administration.30 Emerging data from a recently reported phase-I study indicated that combining ABVD with brentuximab vedotin was associated with a 40% incidence of pulmonary toxicity.31 In contrast, no pulmonary toxicity was observed when brentuximab vedotin was combined with AVD. A randomized study will be required to determine the contribution of brentuximab vedotin-based combination programs in the treatment of newly diagnosed patients with advanced stage cHL. However, RABVD and brentuximab vedotin-AVD represent different strategies that may complement each other, but it remains to be seen whether combining rituximab with brentuximab vedotin plus AVD will be necessary. This question can only be answered in randomized studies.
Acknowledgement

The authors would like to thank Dr Yu Cao for her help in collecting data and preparing this manuscript.

Author contribution

A.Y. designed the study, provided administrative support, provided patient care, collected and analyzed data, and wrote the paper. Y.O. provided patient care, collected and analyzed data and wrote the paper. A.R.C. provided patient care, collected and analyzed data. P.M. A.G., B.P., H.H.C., H.A.M., F.H., J.R., F.S., M.A.F., B.S.D., M.A.R., N.D., L.W.K., S.S.N. and L.E.F. provided patient care. L.F., and Y.Y. analyzed data. All approved final manuscript.

Conflict of Interest Disclosure

A.Y. Research funding (Genentech, Novartis, SBIO, Seattle Genetics, Syndax, Sanofi-Aventis) and honoraria (Novartis, Seattle Genetics, Sanofi-Aventis); Y.O. None; P.M. Advisory board (Genentech); A.C. None; A.G. Research funding (Genentech, ROCHE); B.P. None; L.Feng. None; Y.Y. None; H.C. None; H.M. None; F.H. None; J.R. None; F.S. None; M.F. Research funding (Genentech); B.D None; M.R. Research funding (Pfizer, Glaxo/Smith/Kline); N.D None; L.K. None; S.N. None; L.Fayad None
Table 1. Patient characteristics of 78 eligible patients treated with RABVD

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>RABVD</th>
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<tbody>
<tr>
<td><strong>Total</strong></td>
<td>78</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>40 (51%)</td>
</tr>
<tr>
<td>Female</td>
<td>38 (49%)</td>
</tr>
<tr>
<td><strong>Age, Median (Range) years</strong></td>
<td>32 (18-72)</td>
</tr>
<tr>
<td><strong>Stage</strong></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>28 (36%)</td>
</tr>
<tr>
<td>&gt; 8 cm with B symptoms</td>
<td>3 (4)</td>
</tr>
<tr>
<td>≥10 cm or mediastinal ≥1/3 chest diameter</td>
<td>23 (29%)</td>
</tr>
<tr>
<td>Relapsed after previous primary radiation therapy</td>
<td>2 (3%)</td>
</tr>
<tr>
<td>III</td>
<td>24 (31%)</td>
</tr>
<tr>
<td>IV</td>
<td>26 (33%)</td>
</tr>
<tr>
<td><strong>IPS</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>6 (8%)</td>
</tr>
<tr>
<td>1</td>
<td>19 (24%)</td>
</tr>
<tr>
<td>2</td>
<td>18 (23%)</td>
</tr>
<tr>
<td>3</td>
<td>18 (23%)</td>
</tr>
<tr>
<td>≥4</td>
<td>17 (22%)</td>
</tr>
<tr>
<td><strong>CD20 Status</strong></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>14 (18%)</td>
</tr>
<tr>
<td>Negative</td>
<td>56 (72%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (10%)</td>
</tr>
<tr>
<td><strong>Post-chemotherapy radiation</strong></td>
<td>26 (33%)</td>
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Table 2. Toxicity after RABVD (N=78)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Total</th>
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<tbody>
<tr>
<td>General</td>
<td></td>
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<td></td>
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<tr>
<td>Fatigue</td>
<td>31%</td>
<td>9%</td>
<td>5%</td>
<td>4%</td>
<td>49%</td>
</tr>
<tr>
<td>Pain</td>
<td>10%</td>
<td>23%</td>
<td>6%</td>
<td>0%</td>
<td>40%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>23%</td>
<td>19%</td>
<td>0%</td>
<td>0%</td>
<td>42%</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>37%</td>
<td>19%</td>
<td>8%</td>
<td>0%</td>
<td>64%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22%</td>
<td>15%</td>
<td>1%</td>
<td>0%</td>
<td>38%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13%</td>
<td>9%</td>
<td>0%</td>
<td>0%</td>
<td>22%</td>
</tr>
<tr>
<td>Constipation</td>
<td>13%</td>
<td>12%</td>
<td>0%</td>
<td>0%</td>
<td>24%</td>
</tr>
<tr>
<td>Pulmonary</td>
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<tr>
<td>Cough</td>
<td>10%</td>
<td>9%</td>
<td>0%</td>
<td>0%</td>
<td>19%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>10%</td>
<td>9%</td>
<td>1%</td>
<td>0%</td>
<td>21%</td>
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<tr>
<td>Neurologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neuropathy</td>
<td>24%</td>
<td>6%</td>
<td>1%</td>
<td>0%</td>
<td>32%</td>
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<td>Infection</td>
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<td></td>
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<tr>
<td>Infection</td>
<td>6%</td>
<td>8%</td>
<td>3%</td>
<td>0%</td>
<td>17%</td>
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<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granuloctopenia</td>
<td>3%</td>
<td>8%</td>
<td>15%</td>
<td>8%</td>
<td>33%</td>
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Figure Legends

Figure 1. Study profile

Figure 2. (A) Event free survival and overall survival in all patients. (B) Event free survival by Ann Arbor stage. (C) Event free survival by IPS groups

Figure 3. (A) Event free survival by CD20 status on malignant cells. (B) Event free survival by interim PET result.
Figure 1. Study profile

Registered (N=85)

Ineligible
DLBCL (n=1)
NLPHL (n=1)
Stage I or II non-bulky cHL (n=5)

Eligible (N=78)

Received at least one dose (N=78)

All assessed for toxicity, EFS and OS (N=78)

Received 6 Rituximab (N=76)

Ribuximab < 6 infusion due to non-compliance (N=2)

Response could not be assessed (N=5)

Completed 6 ABVD (N=70)

ABVD less than 6 cycles (N=6)

Early progression (N=1)

Elected 4 ABVD for stage II bulky disease in CR, followed by XRT (N=1)

ABVD 5 cycles due to cytopenia (N=1)

Non-compliance (N=3)

Response assessed N=73
Figure 2

A  
OS and EFS (n=78)

B  
EFS by IPS

C  
EFS by Stage
Figure 3

A  EFS by CD20 expression

- CD20+ (n=14)
- CD20- (n=56)  p = 0.230

B  EFS by interim PET

- PET- (n=52)
- PET+ (n=13)  p = 0.076
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