ABVD plus rituximab *versus* ABVD alone for advanced stage, high-risk classical Hodgkin lymphoma: a randomized phase 2 study

Based on several randomized studies comparing doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) with other multi-drug regimens, ABVD is the standard of care for newly diagnosed, advanced stage, classical Hodgkin lymphoma (cHL).[1] While the cure rate with ABVD approximates 75% in patients with low-risk disease, only 55% of patients with high-risk, advanced cHL, defined as an international prognostic score (IPS) greater than 2, will be disease-free at 3 years, highlighting the need for more effective therapeutic strategies.

In up to 20-30% of patients with cHL, Reed-Sternberg (RS) cells express CD20.[2] CD20 is also expressed on the precursors of RS cells and in B-lymphocytes, exerting a pro-tumoral activity in the tumor microenvironment.[3]

Pre-clinical studies have shown that the anti-CD20 monoclonal antibody rituximab may be an effective therapeutic strategy in cHL, both by direct killing of RS cells and by targeting the surrounding microenvironment.[3,4] As a single agent rituximab has activity in relapsed cHL[5,6] and its combination with ABVD (R-ABVD) as frontline therapy for patients with advanced cHL resulted in a 3-year event-free survival of 77%, with a 22% absolute improvement as compared to historical data with ABVD.[7,8] We present here the results of a multicenter, open-label, randomized, phase 2 study (NCT00654732), comparing R-ABVD to ABVD as initial treatment of patients with advanced stage, high-risk (IPS >2) cHL.

Eligible patients were required to have histologically confirmed, chemotherapy-naïve, advanced-stage cHL (stage III or IV disease), and an IPS >2. The study protocol was approved by the institutional review boards of all institutions involved, and conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent to participation in the study.

R-ABVD and ABVD were given as previously described.[7] The responses were assessed using the 2007 Revised Response Criteria for Malignant Lymphoma (including positron emission tomography but not Deauville criteria; no central review was required per protocol), and toxicity was graded by Common Terminology Criteria for Adverse Event (CTCAE) version 1. Based on a risk of febrile neutropenia of 10-20%, in the case of an absolute neutrophil count <1x10^9/L, the next cycle of treatment was delayed until an absolute neutrophil count >1x10^9/L was reached, and growth factor was added to the following cycles. A tumor was considered positive if any RS cells expressed CD20 by immunohistochemistry.

Based on the results of the original, single-arm, phase 2 study, the primary endpoint was a 22% increase in 3-year event-free survival. Assuming a two-sided type I error rate of 0.05, a trial with 54 patients in each arm was calculated to have 80% power to detect such an increase; unfortunately, because of the low accrual rate, the study was closed prematurely and the target population sample was not reached. Categorical variables were compared using a χ^2 or Fisher exact test. Event-free survival was defined as the time from entry into the study to disease progression, relapse, or death from any cause. Overall survival was calculated from study entry to death from any cause. Survival curves were calculated according to the method of Kaplan and Meier, and compared using the log-rank test. All *P*-values are two-sided and considered statistically significant if ≤0.05 (IBM SPSS 21).

Table 1. Patients' baseline characteristics.

Patients (N=58)	Number (%) R-ABVD (n=26)	ABVD (n=32)
Age, years		
< 45	15 (58)	16 (50)
≥ 45	11 (42)	16 (50)
Male	14 (54)	22 (69)
Female	12 (46)	10 (31)
Stage		
III	4 (15)	9 (28)
IV	22 (85)	23 (72)
International Prognostic Score		
3	13 (50)	13 (41)
≥ 4	13 (50)	19 (59)
RS CD20		
positive	5 (19)	10 (31)
negative	21 (81)	22 (69)

RS: Reed Sternberg cells.

Fifty-eight patients were enrolled between April 2008 and October 2012: 26 were randomized to receive R-ABVD (19% of whom had CD20-positive RS cells), and 32 to receive ABVD (31% of whom had CD20-positive RS cells). The patients' baseline characteristics are shown in Table 1.

The intended six cycles of treatment were completed by 85% of patients in the R-ABVD arm and 84% in the ABVD arm (*P*=0.64). Three patients enrolled in the R-ABVD arm received radiation after this treatment (12% *versus* 0%, *P*=0.08). The overall response rates were 88% and 94% (*P*=0.40) in the two arms, while the complete remission rates were 80% and 81% (*P*=0.64), respectively. Among the patients receiving R-ABVD, no increase in complete remission rate was observed based on whether the patients' RS cells were or were not CD20 positive (80% *versus* 81%, respectively; *P*=0.90).

The most common grade 3-4 toxicities (incidence ≥5%) were neutropenia (50% in the R-ABVD arm *versus* 41% in the ABVD arm; *P*=0.60), anemia (4% *versus* 6%; *P*=1), thrombocytopenia (4% *versus* 6%; *P*=1), infections (15% *versus* 3%; *P*=0.16), respiratory complications (0% *versus* 6%; *P*=0.50), and neuropathy (4% *versus* 9%; *P*=0.62).

After a median follow-up of 67 months (range, 3-113 months), eight (31%) patients progressed in the R-ABVD arm (4 of whom died), and six (19%) in the ABVD arm (2 of whom died). Death in the absence of disease progression was observed in one patient in the R-ABVD arm (total of 9 events) and four patients in the ABVD arm (10 events), and the 3-year event-free survival rates were 63% and 75%, respectively (*P*=0.60) (Figure 1A). The highest 3-year free survival rate (80%) was observed among patients with CD20-positive RS cells treated with R-ABVD, and the lowest (60%) among patients with CD20-negative RS cells treated with the same regimen (Figure 1B).

At the most recent follow-up, five patients (19%) had died in the R-ABVD arm and six (19%) in the ABVD arm. The 3-year overall survival rate was 85% in both groups (*P*=0.94)(Figure 1C). Among patients treated with R-ABVD, the causes of death were known for three

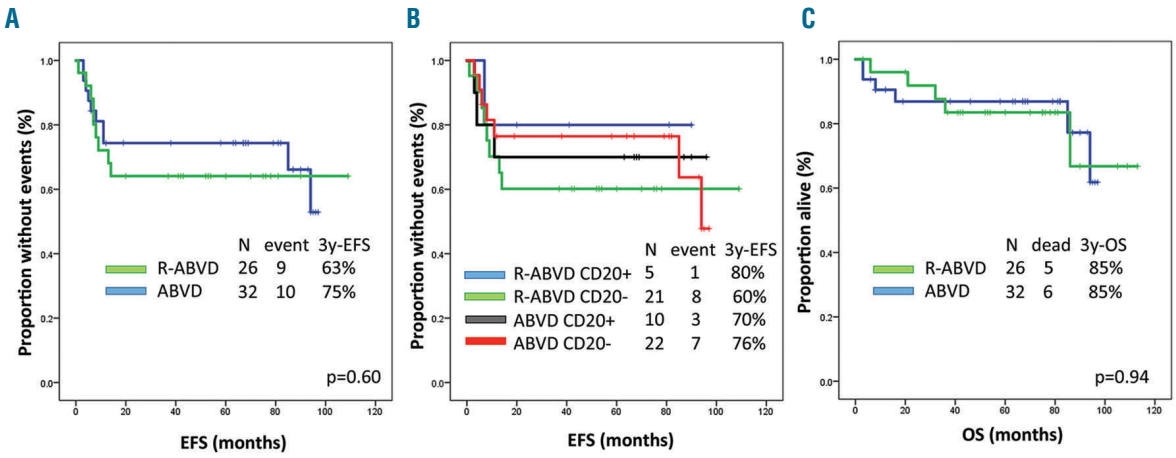

Figure 1. Survival of patients with advanced stage, high-risk classical Hodgkin lymphoma treated with ABVD alone or with ABVD plus rituximab. (A) Event-free survival (EFS) by treatment arm. (B) EFS by treatment arm and CD20 status. (C) Overall survival (OS) by treatment arm. ABVD: doxorubicin, bleomycin, vinblastine, and dacarbazine; R-ABVD: rituximab plus doxorubicin, bleomycin, vinblastine, and dacarbazine.

patients, and were disease progression (n=2) and respiratory failure (n=1); among patients treated with ABVD, the causes of death were known for five patients, and were disease progression (n=2), respiratory failure (n=2) and metastatic esophageal cancer (n=1).

While we acknowledge that its early termination significantly affected the statistical power and quality of the evidence provided, this is the first randomized study comparing R-ABVD to ABVD as initial treatment of patients with advanced stage, high-risk cHL. Despite the promising results observed in previous single-arm, phase 2 studies,[7,8] no significant differences in outcomes were observed with the use of R-ABVD as compared to ABVD, and the primary endpoint of the study was not met. Of interest, similar randomized studies, comparing the combination of rituximab with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) to BEACOPP alone in a similar population also failed to show any improvement in survival.[9,10]

In our study, we observed that patients with CD20-positive RS cells treated with R-ABVD had an increased 3-year event-free survival. While this study was underpowered to detect an increase in event-free survival in CD20-positive cHL, these results suggest that a larger study limited to this population would be useful for ascertaining whether addition of rituximab may improve treatment efficacy in these patients. The malignant cells of the lymphocyte-predominant subtype of Hodgkin lymphoma universally express CD20, and the addition of rituximab to chemotherapy resulted in a 5-year event-free survival of 88.5% in a population with this subtype of lymphoma.[11] No difference in response rate based on CD20 status was observed in the pilot study of single-agent rituximab for the treatment of patients with relapsed cHL.[5] However, in the original, single-arm, phase 2 study of frontline R-ABVD, a higher 3-year event-free survival rate (92% *versus* 77%) was reported for patients with CD20-positive RS cells.[7] While there is a pre-clinical rationale for using rituximab in patients with CD20-negative RS cells, based on CD20 expression on precursor RS cells and pro-tumoral B-lymphocytes,[4,12] further studies focusing only on patients with CD20-positive RS cells may portend better results.

It is important to note that in our study the rate of grade 3-4 neutropenia was higher in the R-ABVD arm than in the ABVD arm, although the difference was not statistically significant. Rituximab can induce immune-mediated neutropenia, increasing the risk of neutropenia and febrile neutropenia associated with the use of ABVD.[13] This may explain the overall shorter event-free survival observed in our study with R-ABVD, as compared to ABVD, despite which the former arm still compared favorably when the analysis was stratified by RS CD20-status.

In addition, RS CD20 status did not affect event-free survival among patients in the ABVD arm, suggesting that its positivity may represent a predictive, rather than a prognostic, factor.

The frontline treatment of patients with advanced stage cHL is quickly moving to targeted therapy. In the phase 3 international ECHELON-1 study, the combination of brentuximab vedotin (BV) with doxorubicin, vinblastine, and dacarbazine (AVD) as frontline treatment in patients with advanced stage cHL met the primary endpoint of increased modified event-free survival.[14] In addition, cohort D of the Checkmate 205 study included patients with newly diagnosed, advanced stage cHL who, after frontline treatment with four cycles of nivolumab, received six cycles of the combination of nivolumab and AVD: the overall response rate of these patients was 86% and their complete remission rate was 80%.[15] Finally, a phase I trial evaluating the combination of nivolumab and BV as frontline treatment for elderly patients with cHL not eligible for chemotherapy is underway (NCT02758). Longer follow-up is needed to demonstrate durability of response with these novel treatment options in the frontline setting.

In upcoming chemotherapy-free trials, the investigation of the activity of rituximab in combination with biological agents and/or immunotherapy is warranted, particularly in patients with CD20-positive RS cells.

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