Bleomycin, vinblastine and dacarbazine combined with nonpegylated liposomal doxorubicin (MBVD) in elderly (≥70 years) or cardiopathic patients with Hodgkin lymphoma: a phase-II study from Fondazione Italiana Linfomi (FIL)

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Abstract

This phase-II study assessed activity and toxicity of substituting conventional doxorubicin with nonpegylated liposomal doxorubicin in the conventional ABVD regimen for the treatment of elderly or cardiopathic patients with HL. Stage I–IIA and IIB–IV patients were treated with three courses of MBVD plus radiotherapy, or six courses of MBVD, respectively, plus radiotherapy limited to bulky or residual disease areas. The primary endpoints were CR rate and the rate of cardiac events. Forty-seven patients were enrolled. Median age was 75 years, 13 had stage I–II disease. Overall, CR was achieved by 36 patients (77%, 95% CI: 62–88), 100% and 68% in stage I–II and III–IV, respectively. With a median follow-up of 40 months (IQR: 36–45). Three-year overall survival (OS) and progression-free survival (PFS) were 70% and 43%, respectively. Cardiac events grades 3–5 were reported in two patients. In conclusion, MBVD’s activity and safety profile was comparable to historical ABVD data.

Introduction

Effective combination chemotherapy regimens, progress in radiotherapy and the introduction of new drugs have dramatically improved the outcome in Hodgkin lymphoma (HL) patients over the last few decades [1]. Although the curability in young patients exceeds 80%, treatment results are still unsatisfactory for older patients, especially for those with advanced disease. The 5-year survival rates for patients 66–80 years or older than 80 are only 55% and 28%, respectively [2].

The poor prognosis in elderly HL patients can partially be explained by features of the disease in this population – more aggressive behavior and an

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impaired immune system – which may contribute to the development of EBV-positive HL [3]. The unfavorable prognosis in the elderly is more likely related to age-specific factors such as the presence of comorbidities and the decreased functional performance of all tissues, which lead to low compliance and increased toxicity to conventional therapies [4,5].

One of the major problems in the elderly with cancer is the cardiac toxicity secondary to the use of anthracyclines, which is considered one of the causes of the high toxicity of ABVD in elderly patients with HL. Nonpegylated liposomal doxorubicin (MyocetTM) has been approved for the treatment of metastatic breast cancer, with more favorable cardiac safety than that of doxorubicin [6], and it has been used successfully to treat diffuse large B-cell lymphoma (DLBCL) in the elderly or in patients with cardiac comorbidity [7–9].

Defining the best treatment strategy for elderly HL patients is difficult because most trials exclude patients older than 65 years, and there are few prospective data in this population. This phase-II study aimed to investigate the efficacy and the safety of an ABVD-like regimen with nonpegylated liposomal doxorubicin instead of conventional doxorubicin in nonfrail elderly patients and in patients with cardiac comorbidity with HL.

Methods and materials

Patient eligibility and treatment

This is a phase-II single-arm open-label multicenter clinical trial. Inclusion criteria were: previously untreated histologically confirmed diagnosis of classic HL (nodular lymphocyte predominance was excluded), age older than 69 years or age 18–69 years with concomitant evident cardiac disease. Patients defined as frail were excluded, as were patients with previous malignant disease or HIV infection. The definition of a frail patient was based on the use of a modified Comprehensive Geriatric Assessment and included one or more grade 3–4 comorbidities according to Cumulative Illness Rating Scale (CIRS-G) scale [10] or the presence of geriatric syndrome; any grade of Activity of Daily Living (ADL) or Instrumental Activity of Daily Living (IADL) score was not a reason for exclusion.

The definition of cardiac disorder, used for the accrual of patients younger than 70 years, was based on the presence of at least one of the following: left ventricular ejection fraction (LVEF) <50%, left ventricular hypertrophy (septal wall and/or posterior wall thickness >1.2 cm), uncontrolled moderate-to-severe arterial hypertension, history of ischemic heart disease, clinically significant ventricular arrhythmia (score 3 according to the Lown grading system), chronic atrial fibrillation, pulmonary hypertension (mean estimating pulmonary artery pressure >45 mmHg), moderate-to-severe mitral valve disorders, moderate aortic valvular disease (mean pressure gradient 20–40 mmHg).

Baseline assessment included medical history, physical examination, serum chemistry, Computer Tomography scan (CT) of chest, abdomen and pelvis, Positron emission computer tomography scan (PET), bone marrow biopsy (BMB), electrocardiogram (ECG) and two-dimensional echocardiogram (2D-ECD). All patients signed informed consent before enrollment. Interim PET after cycle 2 was allowed but not mandatory and was not used to change subsequent treatment.

For early stages (I–IIA), the treatment consisted of three courses of MBVD (MyocetTM 25 mg/m2; bleomycin 10 mg/m2; vinblastine 6 mg/m2; dacarbazine 375 mg/m2 on days 1 and 15 of each course every 28 days) plus involved field (IF) radiotherapy (RT) delivered at 30 Gy. For patients with advanced disease (stage IIB–IV), the treatment consisted of six courses of MBVD and RT limited to sites of initial bulky disease (30 Gy) or residual PET-positive area (36 Gy). Prophylactic use of granulocyte growth factors was recommended; erythropoietin treatment was suggested if hemoglobin values dropped below 11 gr/dl.

The cardiac function was monitored with LVEF and ECG at the end of treatment.

The study was approved by local Ethics Committee and Institutional Review board of each participating centers. The study was registered on ClinicalTrials.gov with number NCT01523847.

Study design and statistics

The two primary endpoints of the study were the Complete Remission (CR) rate according to international criteria [11] and the rate of Cardiac Events (CEs) defined as a reduction of LVEF ≥15% from baseline or the occurrence of any significant cardiac disorder during treatment.

Based on data from the literature, the minimum accepted proportion of CR was 70% and the maximum tolerated cardiotoxicity was 20%. We used the Bryant and Day two-stage design, considering an acceptable efficacy of 0.80 and an acceptable toxicity of 0.05, with an alpha error for efficacy and toxicity of 0.10, power = 0.80. The sample size for the first and second stages was 17 and 47 patients, respectively. Advancement to
the second stage was contingent on achieving at least 13 CR, with no more than 2 patients experiencing cardiac toxicity during the first stage. The MBVD results could be considered positive at the end of the study if there were at least 37 patients in CR and fewer than 7 patients experiencing cardiotoxicity.

Secondary endpoints were progression-free survival (PFS), relapse-free survival (RFS), overall survival (OS) and relative dose intensity (RDI). The PFS was defined as the time from study entry to the time of documented progressive disease or relapse or death from any cause. The RFS was defined from the time of CR assessment to relapse or death or last follow-up examination. The OS was calculated from the date of enrollment to the date of death from any cause or last follow-up evaluation. For each patient, RDI was calculated both for each drug and for the whole regimen (average across drugs within MBVD) for the first three cycles (RDI3) for all patients and for 6 courses for advanced patients who ended their program of 6 cycles (RDI6).

According to the Hryniuk model, RDI was defined as the percentage of the delivered dose intensity divided by the standard dose intensity and was assessed separately for the first three cycles (RDI3) and for all six cycles (RDI6) [12].

Adverse events were categorized and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 and reported only one time that event occurred per patient. Time-to-event variables were analyzed using the Kaplan-Meier method. All the analyses were stratified according to stage at diagnosis (early vs advanced stages).

**Results**

From March 2010 to January 2013, 47 HL patients were consecutively enrolled by 22 Fondazione Italiana Linfomi (FIL) centers; 41 patients were nonfrail elderly subjects (age ≥70) and 6 were patients aged 18–69 with concurrent cardiac disease. The median age was 75 (range 46–84). Thirteen patients (28%) were in early stage and the remaining 34 (72%) in advanced stage. Concurrent cardiac diseases were identified in 24 patients (51%). According to CIRS-G scale, one or more grade 1–3 comorbidities were present in 28 patients (60%). Median LVEF at baseline was 62% (IQR: 57–65). The patients’ clinical characteristics are summarized in Table 1.

**Treatment administration**

Two hundred and eight MBVD courses were delivered to 47 patients. The 13 early-stage patients regularly

| Table 1. Baseline clinical characteristics. |
|------------------------------------------|
| Characteristics                          | All patients | Early stages (I-IIA) | Advanced stages (IIB-IV) |
| Patients, n (%)                          | 47 (100)     | 13 (28)              | 34 (72)                  |
| Age, years                               |              |                      |                          |
| Median (range)                           | 75 (46–84)   | 72 (46–81)           | 75 (61–84)               |
| < 70 years, n (%)                        | 6 (13)       | 3 (23)               | 3 (9)                    |
| Male, n (%)                              | 31 (66)      | 10 (77)              | 21 (62)                  |
| ECOG PS, n (%)                           | 0            | 12 (92)              | 8 (24)                   |
| 1                                       | 19 (40)      | 1 (8)                | 18 (52)                  |
| 2                                       | 8 (17)       | 0 (0)                | 8 (24)                   |
| B-symptoms, n (%)                        | 27 (57)      | 0 (0)                | 27 (79)                  |
| Histologic subtype, n (%)                | 5 (11)       | 1 (8)                | 4 (12)                   |
| Lymphocyte rich predominant              | 24 (51)      | 6 (46)               | 18 (53)                  |
| Nodular sclerosis                        | 12 (25)      | 4 (31)               | 8 (23)                   |
| Mixed cellularity                        | 0 (0)        | 0 (0)                | 0 (0)                    |
| Lymphocyte depletion                     | 6 (13)       | 2 (15)               | 4 (12)                   |
| Moderate/severe diseases (CIRS-G), n (%) |              |                      |                          |
| 0                                       | 19 (40)      | 4 (31)               | 15 (44)                  |
| 1                                       | 15 (32)      | 5 (39)               | 10 (29)                  |
| 2                                       | 8 (17)       | 2 (15)               | 6 (18)                   |
| 3                                       | 4 (9)        | 2 (15)               | 2 (6)                    |
| 4                                       | 1 (2)        | 0 (0)                | 1 (3)                    |
| Heart and coronary diseases (CIRS-G), n (%) | 23 (49)     | 7 (54)               | 16 (47)                  |
| None                                     | 10 (21)      | 1 (8)                | 9 (26)                   |
| Mild                                     | 11 (24)      | 4 (30)               | 7 (21)                   |
| Moderate                                 | 3 (6)        | 3 (8)                | 2 (6)                    |
| Severe                                   | 62 (57–65)   | 60 (56–65)           | 64 (60–65)               |

ITT: Intention-to-treat; ECOG PS: Eastern Cooperative Oncology Group Performance Status; CIRS-G: Cumulative Illness Rating Scale – Geriatric; LVEF: Left Ventricular Ejection Fraction; IQR: Interquartile Range.
completed their planned three courses of chemotherapy, without experiencing any serious adverse event (SAE); combined IF RT was administered in 12/13 early-stage patients, due to treatment refusal in one case. Of the 34 patients with advanced stages, treatment was discontinued in 13 (38%) cases, mainly after cycle 3 (Figure 1): nine due to severe toxicity (four infectious pneumonitis, one pulmonary tuberculosis, one acute coronary syndrome, one acute urinary retention, one fatigue), one due to disease progression, two due to poor compliance or consent withdrawal and one due to lung cancer. Six advanced stage patients received subsequent RT. RDI3 and RDI6 were evaluated for 44 and 21 patients, respectively. Overall, the median RDI3 was 0.92 (IQR: 0.80–1.00) and the median RDI6 was 0.81 (IQR: 0.72–0.93).

### Activity and efficacy

Based on the intention-to-treat (ITT) analysis, 36 patients (77%) achieved CR (minimum and acceptable CR threshold for activity 70% and 85%, respectively), five (11%) obtained a partial response (PR), two (4%) showed a stable disease (SD), three patients (6%) progressed and the last interrupted treatment before response assessment due to the consent withdrawal after the first cycle. CR rates according to early and advanced disease were 13/13 (100%) and 23/34 (68%), respectively.

With a median follow-up of 40 months (IQR: 36–45), all the early-stage patients were alive without any evidence of relapse. Twelve advanced patients died, three of whom due to HL progression; the other nine died due to one of the following causes: three due to acute toxicity (two pneumonia and one heart attack, resulting in a 6.4% treatment-related mortality (TRM)), two of lung cancer diagnosed within 7 months after the end of their treatment, one of pneumonia 1 year after the end of treatment, one of stroke and two, both over age 75 years and with metabolic and cardiac comorbidities, of heart failure and heart attack, respectively, one and three years after the end of treatment, respectively. In summary, acute and late CE with fatal exit occurred in three patients.

For the whole cohort of patients, the three-year OS and PFS were 78% (95%CI: 63–88) and 59% (95%CI: 43–72), respectively. All the early-stage patients were alive, with no evidence of disease. In advanced-stage patients, the 3-year OS and PFS were 70% (95%CI: 51–82) and 43% (95%CI: 26–59), respectively.

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**Figure 1.** Patients flow-chart.

| Enrolled patients (n=47) |
|-------------------------|
| Early stages (IA-IIA) (n=13) |
| Received 3 cycles MBVD (n=13) |
| Received RT (n=12) |
| Treatment discontinuation (n=1) |
| Treatment discontinuation (n=1) |

| Advanced stages (IIB-IV) (n=34) |
|----------------------------------|
| Received 6 cycles MBVD (n=21) |
| Treatment discontinuation (n=13): |
| - Adverse event (n=9) |
| - Progression (n=1) |
| - Poor compliance (n=1) |
| - Consent retirement (n=1) |
| - Second primary malignancy (n=1) |
respectively (Figures 2 and 3). Of the 23 advanced-stage patients who achieved a CR at the end of treatment, the 2-year RFS was 52% (95%CI: 30–70) (Figure 4).

**Toxicity**

Treatment-related toxicities are shown in Table 2. The most common grade 3–4 toxicity was neutropenia, observed in 23 patients (48.9%), while grade 3 anemia
Table 2. Hematological and extra-hematological adverse events.

| Adverse event              | Any grade n (%) | Grade 3 n (%) | Grade 4–5 n (%) |
|----------------------------|-----------------|---------------|-----------------|
| Anemia                     | 26 (55.3)       | 4 (8.5)       |                 |
| Thrombocytopenia           | 12 (25.5)       | 1 (2.1)       |                 |
| Neutropenia                | 28 (59.6)       | 9 (19.1)      | 14 (29.8)       |
| Cardiac                    | 2 (4.3)         | –             | 1 (2.1)         |
| Metabolic                  | 5 (10.6)        | 5 (10.6)      |                 |
| Gastrointestinal           | 16 (34.0)       | –             | 1 (2.1)         |
| Hepatic                    | 1 (2.1)         | 1 (2.1)       |                 |
| Documented infection       | 8 (17)          | 3 (6.3)       | 4 (8.5)         |
| Febrile Neutropenia        | 3 (6.3)         | 3 (6.3)       |                 |
| Neurologic                 | 2 (4.2)         | –             |                 |
| Respiratory                | 4 (8.5)         | –             |                 |
| Renal                      | 2 (4.2)         | –             |                 |
| Other                      | 18 (38.2)       | 2 (4.2)*      |                 |

*1 asthenia, 1 panic attack.

and thrombocytopenia were reported in 4 (8.5%) and 1 (2.1%) patients, respectively. Seven (14.8%) patients had grade 3–5 infections or grade 3 febrile neutropenia (6.3%). Bleomycin lung toxicity was observed in only one patient.

Overall, according to the co-primary endpoint, cardiotoxicity was observed in 2 patients (4.3%) (maximum and acceptable cardiotoxicity threshold for safety 20% and 5%, respectively), including one case with LVEF reduction of 15% (CTCAE grade 2) after six cycles and one fatal cardiac ischemia. This patient was a 76-year-old woman with a medical history of diabetes mellitus, arterial hypertension and cardiac comorbidity. She was admitted to the hospital for atrial arrhythmia and congestive heart failure after the administration of the fourth cycle and died a few days later. In addition, one patient experienced a transient LVEF reduction after 4th MBVD that was not confirmed at the end of RT or during follow-up.

Although the echocardiogram at the end of the chemotherapy program was mandatory, it was performed in only 17 of the 21 advanced patients who received six cycles of MBVD. In this subgroup of patients, the average median LVEF decrease from baseline to the end of study was 3% (IQR: –7, 4).

Discussion

ABVD is regarded as the standard treatment for non-frail elderly patients with HL [13,14]. The results, however, are inferior to those in younger patients, mainly because of the high toxicity, poor compliance, the need to reduce RDI and the frequent early interruption of treatment. Major concerns are cardiac, lung and infectious toxicities.

Recently, Böll et al. (2013) reported data on the efficacy and safety of four cycles of ABVD plus IF RT in 117 early-stage HL patients aged 60–75 years, enrolled in the German HD10 and HD11 trials. One or more WHO grade 3–4 toxicities during chemotherapy were observed in 68% of patients, compared to only 50% in younger patients enrolled in the same trials. Acute TRM of older patients was 5%, and only 59% of those aged 60–75 received an RDI of at least 80. The 5-year PFS and OS rates were 75% and 81%, respectively, which compare unfavorably to those achieved in younger patients [15]. In addition, we must consider that this is a trial on a selected group of relatively young patients (i.e. a median age of 65 years).

The same author subsequently analyzed the results of the HD10 and HD13 trials and compared the efficacy and toxicity of two courses of ABVD with four courses. In this setting, again given the selected, relatively young patients, a significant bleomycin-induced lung toxicity (BLT) occurred in 10% of patients randomized to four ABVD, compared with only 1.5% in patients treated with two ABVD only [16]. CR rates in patients receiving two cycles of chemotherapy ranged between 96% and 99%, compared to only 88% after four ABVD, partially because of the higher TRM. ABVD chemotherapy therefore seems acceptable in terms of tolerance and toxicity only when a limited number of courses is administered. In our study, the thirteen early-stage patients regularly ended the three planned courses of chemotherapy, and only one patient refused the subsequent IF RT. No severe lung or cardiac toxicities were registered in this subgroup of patients. The CR rate was 100%. After a median follow-up of 40 months, all patients were alive and disease-free. Three courses of ABVD therefore proved to be effective and well tolerated even in a group of very old patients, whose median age was 72 years.

The efficacy and tolerability of the less intensive VEPEMB regimen was evaluated in two recent prospective studies. In the SHIELD study, 103 nonfrail patients (median age 73 years, range 61–85 years) selected according to the SGNLG-modified ACE-27 comorbidity scale were treated with the VEPEMB.
regimen. For advanced-stage patients, the CR rate was 61%, the 3-year OS and PFS rates were 66% and 58%, respectively, and the TRM was 7%. A subgroup of 35 patients did not enter the trial and were treated with ABVD based on the physician’s opinion. In this small subgroup, the TRM due to septic events was 11% and the CR rate was only 51% [17]. Although ABVD and VEPEmb subgroups are not perfectly comparable in this study because of the initial selection bias, the results could not demonstrate the superiority of ABVD over VEPEmb in elderly patients. A second phase III study from the FIL showed that in patients aged 65-80 years identified as nonfrail according to the CIRS scale, the CR, 5-year OS rate and the 5-year PFS rate were better in the ABVD than in the VEPEmb arm: 96% vs 85%, 77% vs. 63% and 70% vs 48%, respectively. This difference was not significant, however, mainly due to the low number of patients. Treatment violations or interruptions were more frequent in the ABVD arm than in the VEPEmb arm (26% vs 12%, p = ns). The concomitant lower efficacy and better tolerance of VEPEmb in comparison to ABVD probably depended on the absence of doxorubicin in the VEPEmb regimen [14].

Two other nonrandomized retrospective studies have suggested a favorable role of doxorubicin. The first study compared ChIVPP (chlorambucil, vinblastine, procarbazine and prednisone) with the hybrid ChIVPP/ABV (added doxorubicin, bleomycin and vincristine) in 56 patients over age 60 years. The 5-year EFS and OS rates were significantly better with the hybrid regimen (24 vs 52%; p = .011; 30% vs 67% p = .0086, respectively) [18]. In the Swedish study, the patients who received ABVDbased chemotherapy with RDI >65% had better OS than patients who were given the same chemotherapy with RD \leq 65% or MOPP-like therapy regardless of its RDI (p = .001) [19].

Antracyclin-based regimens should therefore be considered the best first-line treatment for HL, although their use may be limited by cardiotoxicity, especially in elderly patients and in patients with cardiac comorbidities.

To reduce anthracycline toxicity in elderly or cardiopathic patients, we replaced doxorubicin in the classic ABVD regimen with nonpegylated liposome doxorubicin (Myocet™). Preclinical studies have shown that, compared to conventional doxorubicin, delivery of liposomal doxorubicin is higher through the disrupted capillaries of the tumor tissues, while both peak and overall concentrations are reduced by 30–40% in myocardial tissue. This diminished myocardial exposure resulted in a significant reduction of both functional and histological cardiac toxicity [20,21]. Two randomized studies on patients with metastatic breast cancer confirmed that liposomal-encapsulated doxorubicin has the same efficacy as and a significantly better cardiac safety profile than conventional doxorubicin [6,22]. Moreover, the use of liposomal encapsulated doxorubicin has recently been tested, with encouraging results in patients with DLBCL not eligible for conventional chemotherapy because of advanced age, cardiac comorbidity or pretreatment with anthracyclines [7,8].

In our MBVD study, 68% of advanced-stage patients achieved CR, and the 3-year OS and PFS rates were 70% and 43%, respectively. The cumulative percentage of cardiac events was 4.3%. These data compare favorably with other anthracycline-based regimens. In the COPP/ABVD arm of the HD9 elderly study, grade 3–4 cardiac events were 8% [23]. Four out of 57 patients (7%) treated with PVAG (prednisone, vinblastine, doxorubicin, gemcitabine) experienced severe cardiac toxicity [24]. Treatment interruption due to cardiotoxicity was reported in 3 out of 27 patients (11%) enrolled in the ABVD arm of the FIL study [14]. The replacement in the ABVD regimen of classical doxorubicin with liposome-encapsulated doxorubicin resulted, therefore, in a favorable profile in terms of cardiotoxicity. Moreover, the acute TRM of 6.4% favorably compared with the results of other doxorubicin-based studies on elderly patients, where toxic deaths reported were between 9% and 15.3% [17,23,25].

In advanced-stage patients, however, the overall tolerability of MBVD from the 4th to the 6th course was poor, with 38% of this subgroup of patients obliged to prematurely discontinue treatment due to a toxic event or poor compliance. This high dropout rate could be explained by the advanced age of patients (median 75 years; range 46–84 years) and by the fact that only frail patients were excluded, while those with reduced ADL and IADL scores and a relatively high number of comorbidities were accepted. As a consequence of the global toxicity and reduction in planned strategy, the final results in terms of PFS and OS still remain unsatisfactory in advanced-stage patients. Selective strategies based on age stratification and a more stringent evaluation of patient frailty based on ADL, IADL and comorbidity scores should be considered to better identify patients who are likely to tolerate a full course of curative chemotherapy.

A new frontline treatment option might be brenuximab vedotin (BV), a CD30-directed drug conjugate that is already approved for patients not eligible for or failing autologous stem cell transplant. BV has been
tested in elderly HL patients either alone, in combination or in sequence with chemotherapy, with good activity results and manageable safety profile [26–28]. In the recently published ECHELON1 [29] phase-III trial, a combination of BV + AVD was associated with a significant reduction in pulmonary toxicity but with higher rates of febrile neutropenia and peripheral neuropathy compared to ABVD, and with nonimprovement in terms of modified PFS for the subgroup of elderly patients. The role of BV as frontline therapy in elderly patients was explored in two phase-II studies. In the first one Fossa et al. [30] treated 50 HL patients older than 60 years with the B-CAP regimen (brentuximab vedotin, cyclophosphamide, doxorubicin and prednisolone); the CT-based ORR was 98% with 21 patients having CR. All patients with CT-based CR and 10/26 patients with PR had a negative PET, resulting in a complete metabolic response rate of 65%. Dose delivery was high with only two patients stopping treatment after four and five cycles, respectively, due to toxicity. In the second study Evens et al. treated 48 HL patients, median age of 69 years, with a sequential regimen of two initial doses of single BV followed by six cycles of AVD and four consolidative doses of BV [31]. Study results (CRR 90%, 2-year PFS and OS of 84% and 95%, respectively) are the best ever achieved with the treatment of elderly HL and suggests that sequential use of active drugs might represent an excellent strategy to increase treatment efficacy.

In conclusion, although we were not able to confirm the hypothesis that MBVD regimen could improve results achieved with standard ABVD, the use of nonpegylated liposomal doxorubicin can be considered an active and safe alternative to conventional doxorubicin to treat elderly patients with HL who are not good candidates for standard ABVD due to heart problems or who have a high risk of developing cardiac toxicity. With MBVD, high curability rates are achieved in early stages elderly HL; conversely, management of advanced stage HL in the elderly patient is confirmed as an unmet need for hematologists, and new treatment options with a better risk/benefit profile are strongly warranted.

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