bjh research paper

Reduced intensity VEPEMB regimen compared with standard ABVD in elderly Hodgkin lymphoma patients: results from a randomized trial on behalf of the Fondazione Italiana Linfomi (FIL)

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Summary

Survival rates for elderly Hodgkin Lymphoma (HL) have not improved substantially in recent years, mainly because of a lack of prospective randomized studies, due to difficulties in enrolling patients. Between 2002 and 2006, 54 untreated HL patients, aged between 65 and 80 years and considered 'non-frail' according to a comprehensive geriatric evaluation, were enrolled into a phase III randomized trial to compare a reduced-intensity regimen (vinblastine, cyclophosphamide, procarbazine, prednisone, etoposide, mitoxantrone, bleomycin; VEPEMB) with standard ABVD (adriamycin, bleomycin, vinblastine, dacarbazine). Primary endpoint was progression-free survival (PFS). Seventeen patients were in early stage (I-IIA), while 37 were advanced stage. Median age was 72 years and median follow-up was 76 months. Five-year PFS rates were 48% vs. 70% [adjusted Hazard ratio (HR) = 2·19, 95% confidence interval (CI) = 0·94–5·10, $P = 0·068$] and 5-year overall survival (OS) rates were 63% vs. 77% (adjusted HR = 1·67, 95% CI = 0·69–4·03, $P = 0·254$) for VEPEMB compared to ABVD. Overall treatment-related mortality was 4%. World Health Organization grade 4 cardiac and lung toxicity occurred in four patients treated with ABVD *versus* no cases in the VEPEMB arm. Standard ABVD regimen resulted in better PFS and OS than the VEPEMB, although the differences were not statistically significant. The low toxicity of both treatments was probably attributable to stringent selection of patients based on a Comprehensive Geriatric Assessment that excluded frail patients.

Keywords: elderly, Hodgkin Lymphoma, randomized study.

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Introduction

Owing to the introduction of multiagent chemotherapy schedules and optimization of radiation techniques, Hodgkin lymphoma (HL) is now one of the most curable haematological malignancies. This is particularly true in younger patients, in whom the probability of long-term remission is now 80–90%, considering first-line chemotherapy and salvage with stem cell transplantation. However, these impressive results have not yet been extended to elderly patients. In fact, the prognosis of HL patients aged over 60 years is considerably poor and only modest improvements have been observed over time (Klimm *et al*, 2007; Evens *et al*, 2008); this is mainly due to the fact that elderly patients rarely tolerate conventional chemotherapy regimens, so they are more likely to receive suboptimal doses of chemotherapy, resulting in more treatment failures and relapses (Levis *et al*, 1994; Landgren *et al*, 2003). Recent studies have highlighted the difference in survival rates between older and younger patients, even when administering the same regimen (Ballova *et al*, 2005; Evens *et al*, 2013).

The poor outcome of older patients cannot be explained only by aging, and it is interpreted as a multifactorial process. Patient-related comorbidities have been identified as a prognostic factor that is even more important than age itself, and the evaluation of co-morbidity scales and patient frailness has been proposed to predict the future tolerance of treatment and the clinical outcome (Repetto & Comandini, 2000; Levis *et al*, 2004).

As observed in other types of malignancies, the application of a multidimensional approach is important in order to identify more suitable chemotherapy regimens for elderly patients. The Comprehensive Geriatric Assessment (CGA) has been recently proposed as a valid instrument to support medical decisions for elderly lymphoma patients (Balducci & Beghe, 2000; Extermann & Hurria, 2007).

Given the fact that standard chemotherapy regimens commonly used in younger patients cannot be applied to the older population as a whole, one matter of concern is the selection of patients who can tolerate conventional treatment compared to those who need less toxic regimens or even a palliative approach. A previous phase II study using the VEPEMB (vinblastine, cyclophosphamide, procarbazine, prednisone, etoposide, mitoxantrone, bleomycin) chemotherapy schedule, an original reduced-intensity regimen intended for HL elderly patients, showed good results in terms of feasibility, toxicity and efficacy (Levis *et al*, 2004). A non-randomized study by the UK cooperative group (Proctor *et al*, 2012) also confirmed the encouraging results obtained with this regimen.

The purpose of this study was to randomly compare the VEPEMB regimen *versus* standard ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) in patients older than 65 years, who were considered fit according to an initial comprehensive geriatric evaluation.

Patients and methods

This study was a phase III, open-label, two-arm, randomized prospective multicentre clinical trial. It was approved by the Local Research Ethics Committee and was executed in accordance with the Declaration of Helsinki, Good Clinical Practice, local ethical and legal requirements. The study was registered as EUDRACT number 2004-002097-36.

Eligibility criteria

Patients aged between 65 and 80 years with a biopsy-proven HL, any stage (defined according to the Ann Arbour Conference Classification) and previously untreated were considered eligible for the study. Patients were ineligible if they were positive for the human immunodeficiency virus (HIV), had a concomitant other neoplasm or altered renal (creatinine clearance < 1·169 ml/s), liver (serum bilirubin > 34·2 μmol/l), cardiac (Ejection Fraction < 50%) or pulmonary (diffusion capacity > 25% lower than normal predicted value) function.

In addition, patients underwent a geriatric assessment including: co-morbidity according to the Cumulative Illness Rating Scale (CIRS; Miller *et al*, 1992), index of Activities Daily Living (ADL; Rinaldi *et al*, 2003), index of Instrumental Activity of Daily Living (IADL) and Geriatric Depression Scale (GDS) (Katz *et al*, 1963).

Patients were defined as frail and excluded from the study, when one or more of the following conditions were present:

1 Age higher than 80 years.
2 Three or more grade 3 comorbidities or one or more grade 4 comorbidities according to the CIRS scale.
3 ADL score <6.
4 Geriatric syndrome, defined by the presence of one or more of the following items: dementia, delirium, depression symptoms, carelessness, falls, osteoporosis, bladder and gut control problems.

Each eligible patient was requested to provide a written informed consent.

Study design, randomization and treatment

This was a randomized, multicentre, open-label study that compared the efficacy and the safety of VEPEMB regimen *versus* standard ABVD regimen in eligible HL patients aged 65–80 years.

The VEPEMB schedule was administered as previously reported (Levis *et al*, 2004): vinblastine 6 mg/m^2 intravenously (i.v.), day 1; cyclophosphamide 500 mg/m^2 i.v., day 1; procarbazine 100 mg/m^2 orally (p.o.), days 1–5; prednisone 30 mg/m^2 p.o., days 1–5; etoposide 60 mg/m^2 p.o., days 15–19; mitoxantrone 6 mg/m^2 i.v., day 15 and bleomycin 10 mg/m^2 i.v., day 15. Each course was repeated every

28 days. ABVD (adriamycin 25 mg/m^2, bleomycin 10 mg/m^2, vinblastine 6 mg/m^2 and dacarbazine 375 mg/m^2) was given on days 1 and 15. Both regimens were scheduled every 28 days.

According to Ann Arbour staging system, patients with stage I/IIA disease were allocated to receive three courses of chemotherapy followed by involved field radiotherapy, while stage IIB-IV patients were scheduled to receive six courses followed by radiotherapy limited to the areas of residual masses or previous bulky disease.

Involved field radiotherapy was delivered to the region of initial bulky disease at the dose of 20 Gray (Gy), with a boost of 36 Gy in cases of suspected persistence of disease. The treatment study plan is detailed in Fig 1.

As supportive measures, antibiotic, antifungal prophylaxis and granulocyte colony-stimulating factor (G-CSF) administration were recommended in case of prolonged neutropenia, according to National Cancer Institute (NCI) criteria (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf); erythropoietin was suggested when the haemoglobin level fell below 100 g/l. The study was approved by the ethics committees of each participating centre. Registration forms were sent to the offices of the Haematology Department of Alessandria (Italy); after eligibility criteria evaluation, patients were stratified by stage (I-IIA, IIB-IV) and then randomly assigned to receive VEPEMB or standard ABVD regimen at a 1:1 ratio, using a computer-generated random sequence.

Response and outcome assessment

Response evaluation included physical examination and complete blood cell count before each cycle of chemotherapy and computerized tomography (CT) scan of the chest and abdomen after the third cycle of chemotherapy and at the end of the study. Adverse events were assessed according to the NCI Common Terminology Criteria for Adverse Events, version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).

A clinical and laboratory follow-up was performed at 3-month intervals in the first 2 years and afterwards at 6-month intervals; a CT scan of chest and abdomen was requested yearly for the first 5 years. All instrumental tests were evaluated by the local referee radiologist, eventually

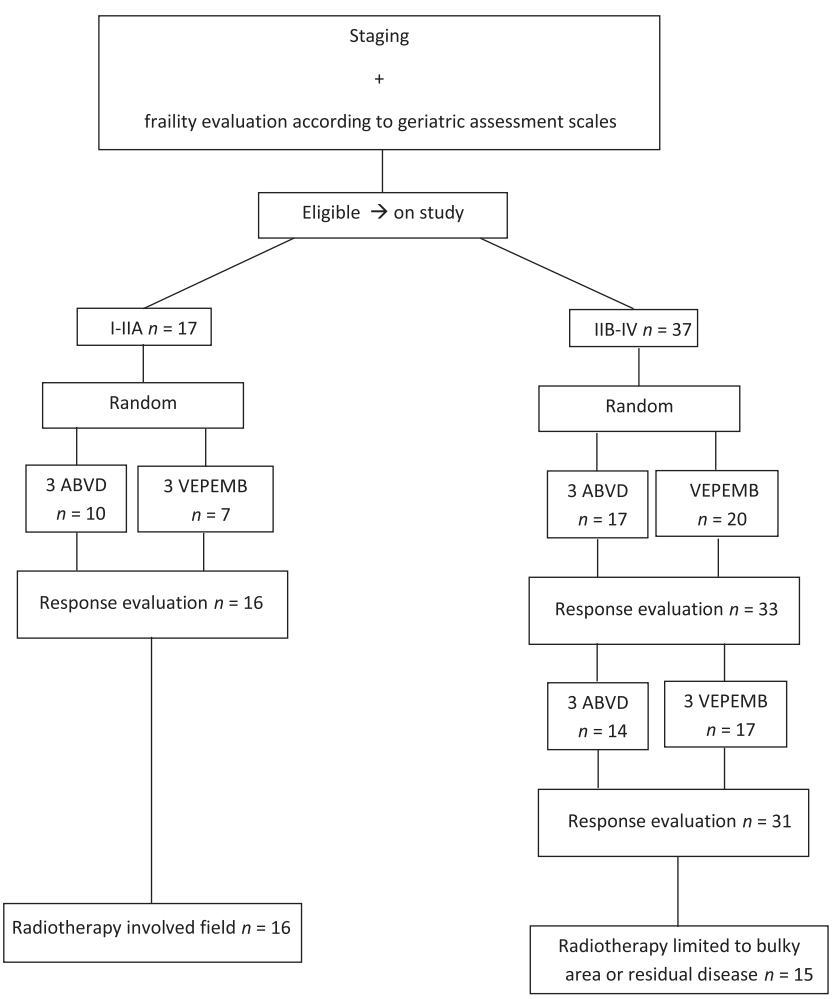

Fig 1. Treatment study plan. ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; VEPEMB, vinblastine, cyclophosphamide, procarbazine, prednisone, etoposide, mitoxantrone, bleomycin.

with the collaboration of the haematologist involved in the study. Radiographic central revision of CT or gallium scan was not scheduled.

When the randomized trial was launched in 2002, [^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) was emerging as a promising, although still experimental, surrogate instrument for determining tumour chemosensitivity and outcome. Therefore PET scan was not considered as mandatory in the clinical staging and evaluation of response; PET or gallium scan was recommended only in cases with residual masses at the end of treatment, in order to better define the presence of active disease.

All responses have been reclassified according to International Working Group (IWG) criteria (Cheson *et al*, 2007).

At the time of writing the protocol, the original end-point was failure-free survival (FFS), defined as time from randomization to the occurrence of one of the following events: lack of remission, relapse, death from any cause, interruption or discontinuation of treatment. Accordingly, the sample size was originally assessed on the basis of the main study outcome. Assuming a FFS of 60% at 3 years for the patients randomized to ABVD, a sample size of 186 patients (93 for each arm) was initially required in order to show a FFS of 75% or more in the VEPEMB arm, with an α error of 0·05 (2-sided) and a β error of 0·20 and an accrual of 4 years.

However, due to increasing difficulties in enrolling patients, during the recruitment period it was evident that the study could not be completed with the sample size and power originally planned. Therefore the study was stopped at 25 July 2011, 61 months since the first patient accrued, before reaching the number of patients and the statistical power needed to detect the expected difference between the two arms.

Considering the recent IWG response criteria (Cheson *et al*, 2007), at the time of drawing the clinical results we decided to update the definition of the primary outcome of the protocol, from FFS to progression-free survival (PFS), measured from date of randomization until lymphoma progression or death as a result of any cause. This change was done according to standard protocol recommendation guidelines (Chan *et al*, 2013). Overall survival (OS), measured from randomization to death of any cause, was considered as the secondary end-point.

Statistical analysis

Progression-free survival and overall survival analyses were carried out in the intention to treat population (ITT), corresponding to all randomized patients. All analyses of time-to-event endpoints (PFS, OS) were performed using the Kaplan–Meier method, with log-rank tests to assess differences between groups. Cox models were used to estimate the effect of VEPEMB *versus* ABVD in terms of hazard ratio (HR), adjusted for most patients and clinical characteristics (gender, age, performance status, stage, systemic symptoms, histology and presence of bulky disease).

Data were centrally collected, entered into a computerized database and analysed using SAS (version 8.2) (SAS Institute, Cary, NC).

Results

Main patient characteristics

Between 2002 and 2006, 54 elderly patients admitted to ten Italian haematological centres belonging to the Fondazione Italiana Linfomi (FIL) network were enrolled into the study. Median age for both treatment groups was 72 years [inter quartile range (IQR): 69–75 years]; 16 patients were over 75 years old.

Twenty-seven patients (50%) were randomly assigned to ABVD and 27(50%) to VEPEMB. Seventeen patients (31%) were classified as early stage and the remaining 37 ones (68%) as advanced stage; one or more comorbidities were present in 39 (72%) cases; 23 patients (43%) had the mixed cellularity subtype and 26 (47%) had nodular sclerosing HL. No relevant differences were observed between the two arms in terms of gender, stage, histology, comorbidity and IADL, as shown in Table I.

Efficacy

Overall, a complete response (CR) was observed in 49 patients (91%); at a median follow-up of 76 months (IQR 62–95), 5-year PFS and OS rates were projected at 59% and 70%, respectively.

Stratifying the population according to early (16 patients) *versus* advanced disease (17 patients), CR was seen in 93% vs. 63%, with 5-year PFS rates of 76% vs. 51% ($P = 0{\cdot}05$) and OS rates of 76% vs. 70% ($P = 0{\cdot}26$), respectively.

The overall response rate (ORR) was slightly worse in the VEPEMB arm than in the ABVD arm (88% vs. 96%, $P = 0{\cdot}6$) (Table II).

Overall, 23 (42·6%) patients have died so far, 14 (52%) in the VEPEMB arm and 9 (33%) in the ABVD arm. Causes of death were as follows: (i) after VEPEMB: 8 HL-related deaths, 2 deaths for unknown reasons, secondary neoplasia in 2 patients, one treatment-related mortality (TRM), one death from pneumonia after salvage treatment for recurrent disease, (ii) after ABVD: 4 deaths due to disease progression, 3 cases of secondary neoplasia, one TRM and one cerebral stroke a year after the end of treatment.

Five-year PFS rates for VEPEMB *versus* ABVD were 48% vs. 70%, with an adjusted HR of 2·19 (95% CI = 0·94–5·10, $P = 0{\cdot}068$) (Fig 2 and Table III). Corresponding results for OS were 63% vs. 77% (adjusted HR = 1·67, 95% CI = 0·69–4·03, $P = 0{\cdot}254$) (Fig 3 and Table IV).

Both unadjusted and adjusted analyses suggested a worse outcome for patients randomized to the VEPEMB arm, even if the differences were not statistically significant (Tables III,

Table I. Patient and clinical characteristics at the time of enrolment by treatment.

Variables	ABVD ($N = 27$) N (%)	VEPEMB ($N = 27$) N (%)	Total N (%)	P
Gender				
Female	13 (48·1)	14 (51·9)	27 (50)	0·78†
Male	14 (51·9)	13 (48·1)	27 (50)	
Age, years				
Median (IQR)	72 (68–75)	72 (69–75)	72 (69–75)	0·99§
ECOG PS				
0	20 (74·1)	16 (59·3)	35 (64·8)	0·29†
1–2*	7 (25·9)	11 (40·7)	18 (33·4)	
IADL				
1–7	7 (25·9)	10 (37)	17 (31·5)	0·38†
8	20 (74·1)	17 (63)	37 (68·5)	
Comorbidity				
No	9 (33·3)	6 (22·2)	15 (27·8)	0·36†
Yes	18 (66·7)	21 (77·8)	39 (72·2)	
0	9 (33·3)	6 (22·2)	15 (27·8)	
1	9 (33·3)	8 (29·7)	17 (31·5)	
≥2	9 (33·4)	13 (48·1)	22 (40·7)	
Stage				
I-IIA	10 (37)	7 (26)	17 (31·5)	0·38†
IIB-IV	17 (63)	20 (74)	37 (68·5)	
Systemic symptoms				
No	14 (51·8)	12 (44·4)	26 (48·2)	0·59†
Yes	13 (48·2)	15 (55·6)	28 (51·8)	
Bulky				
No	21 (77·8)	18 (66·7)	39 (72·2)	0·36†
Yes	6 (22·2)	9 (33·3)	15 (27·8)	
Histology				
Missing	–	1 (3·7)	1 (1·9)	0·84‡
LP	1 (3·7)	1 (3·7)	2 (3·7)	
Nodular sclerosis	15 (55·6)	11 (40·7)	26 (48·1)	
Mixed cellularity	10 (37)	13 (48·2)	23 (42·6)	
LRCHL	1 (3·7)	1 (3·7)	2 (3·7)	

ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; VEPEMB, vinblastine, cyclophosphamide, procarbazine, prednisone, etoposide, mitoxantrone, bleomycin; IQR, interquartile range; ECOG PS, Eastern cooperative Oncology Group performance score; IADL, index of Instrumental Activity of Daily Living; LP, lymphocyte predominant; LRCHL, lymphocyte-rich classical Hodgkin lymphoma.
*Number of patients with PS = 2 is two.
†Chi square test.
‡Fisher's exact test.
§Wilcoxon Two-Sample Test.

IV). Similarly, none of the analysed factors was found to be significantly associated with either PFS or OS.

Chemotherapy delivery, dose adjustment and toxicity

All but one of the patients in early stage disease received the full planned number ($n = 3$) of cycles. In advanced stage disease, six cycles of chemotherapy were delivered to 14 patients (82%) in the ABVD arm and to 18 patients (90%) in the VEPEMB arm; treatment interruptions were requested in 2 patients in the VEPEMB arm (for gastrointestinal bleeding and pneumonia) in comparison to 3 patients in the ABVD arm (acute heart failure, atrial fibrillation and non-specified serious event of cardiotoxicity), but this difference was not statistically significant ($P = 0·386$). Dose reductions were requested in 3 patients (6%) treated with ABVD and 4 patients (7%) treated with VEPEMB. Dose adjustments were mainly made as a consequence of World Health Organization (WHO) grade 4 haematological toxicity; in 2 cases bleomycin was withdrawn when fever suddenly occurred after drug infusion.

There were 2 toxic deaths, one occurred in the VEPEMB arm (pneumonia) and one in ABVD arm (acute heart failure), resulting in a overall TRM of 4%.

Table II. Treatment response.

Response	Treatment: ABVD $N = 27$ N (%)	Treatment: VEPEMB $N = 27$ N (%)	P*
ORR	26 (96·3)	24 (88·9)	0·6
CR+CRu	26 (96·3)	23 (85·2)	
PR	–	1 (3·7)	
PD	1 (3·7)	3 (11·1)	

ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; VEPEMB, vinblastine, cyclophosphamide, procarbazine, prednisone, etoposide, mitoxantrone, bleomycin; ORR, overall response rate; CR, complete response; CRu, unconfirmed complete response; PR, partial response; PD, progressive disease.
*Fisher's exact test.

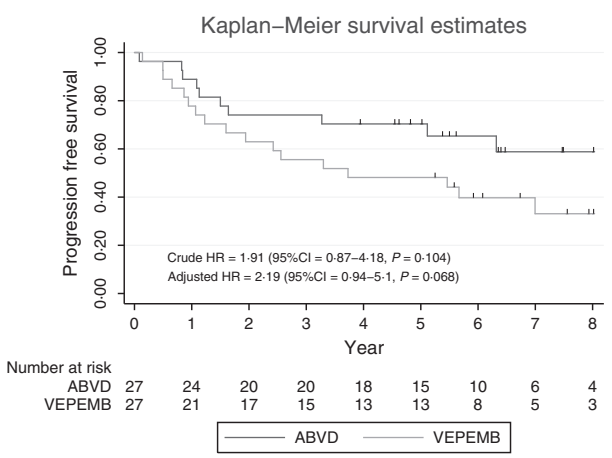

Fig 2. Progression-free survival by treatment. ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; VEPEMB, vinblastine, cyclophosphamide, procarbazine, prednisone, etoposide, mitoxantrone, bleomycin; HR, Hazard ratio; 95% CI, 95% confidence interval.

Table III. Cox proportional hazards analysis of progression-free survival.

	Unadjusted		Adjusted	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Treatment				
ABVD	1·00		1·00	
VEPEMB	1·91 (0·87–4·18)	0·104	2·19 (0·94–5·1)	0·068
Gender				
Female	1·00		1·00	
Male	1·08 (0·47–2·64)	0·855	1·62 (0·63–4·15)	0·316
Age	1·04 (0·95–1·15)	0·403	1·08 (0·97–1·21)	0·170
Performance status				
0	1·00		1·00	
≥1	1·19 (0·53–2·65)	0·670	0·779 (0·31–1·96)	0·595
Stage				
I-IIA	1·00		1·00	
IIB-IV	2·65 (1·00–7·02)	0·049	2·82 (0·79–10·06)	0·110
Bulky				
No	1·00		1·00	
Yes	1·39 (0·61–3·19)	0·436	1·22 (0·47–3·13)	0·686
Systemic symptoms				
A	1·00		1·00	
B	2·04 (0·87–4·83)	0·102	1·09 (0·38–3·12)	0·869
Histology				
Other	1·00		1·00	
NS	0·89 (0·39–2·01)	0·777	0·46 (0·18–1·18)	0·106

HR, Hazard ratio; 95% CI, 95% confidence interval; ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; VEPEMB, vinblastine, cyclophosphamide, procarbazine, prednisone, etoposide, mitoxantrone, bleomycin; NS, nodular sclerosing.

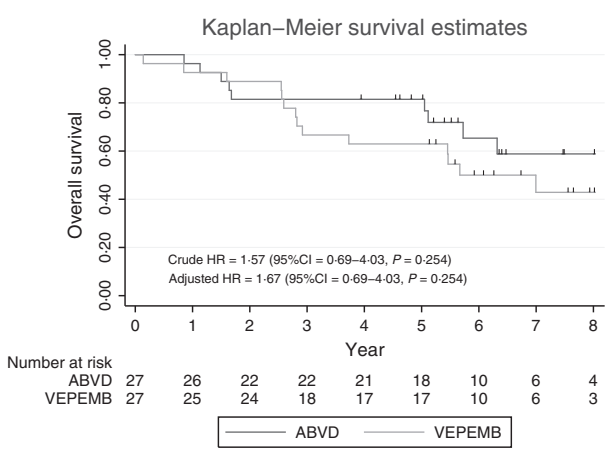

Fig 3. Overall survival by treatment. ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; VEPEMB, vinblastine, cyclophosphamide, procarbazine, prednisone, etoposide, mitoxantrone, bleomycin; HR, Hazard ratio; 95% CI, 95% confidence interval.

WHO grade 4 infection events were recorded in 2 patients in the VEPEMB arm (pneumonia and soft tissue cellulitis) and in 2 patients in the ABVD arm (pneumonia and severe mucositis).

Cardiotoxicity was a matter of concern in the ABVD group: as mentioned above, beside the case of fatal heart failure, two other patients had to stop the planned treatment schedule after the first cycle due to atrial fibrillation and non-specified serious event of cardiotoxicity, respectively; no cardiotoxic events were reported in the VEPEMB arm.

Table IV. Cox proportional hazards analysis of overall survival.

	Unadjusted		Adjusted	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Treatment				
ABVD	1·00		1·00	
VEPEMB	1·57 (0·68–3·62)	0·294	1·67 (0·69–4·03)	0·254
Gender				
Female	1·00		1·00	
Male	1·10 (0·48–2·51)	0·815	1·40 (0·50–3·9)	0·520
Age	1·08 (0·97–1·9)	0·146	1·12 (0·99–1·27)	0·060
Performance status				
0	1·00		1·00	
≥1	1·50 (0·65–3·48)	0·340	1·23 (0·49–3·09)	0·659
Stage				
I-IIA	1·00		1·00	
IIB-IV	1·75 (0·65–4·72)	0·270	1·31 (0·30–5·65)	0·721
Bulky				
No	1·00		1·00	
Yes	1·43 (0·60–3·39)	0·412	1·20 (0·46–3·16)	0·709
Systemic symptoms				
A	1·00		1·00	
B	1·82 (0·77–4·29)	0·173	1·48 (0·41–5·36)	0·552
Histology				
Other	1·00		1·00	
NS	1·01 (0·44–2·29)	0·980	0·85 (0·32–2·25)	0·750

HR, Hazard ratio; 95% CI, 95% confidence interval; ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; VEPEMB, vinblastine, cyclophosphamide, procarbazine, prednisone, etoposide, mitoxantrone, bleomycin; NS, nodular sclerosing.

Bleomycin lung toxicity (BLT) occurred in one patient in the ABVD arm. He was admitted to hospital few days after the sixth cycle of chemotherapy for acute dyspnoea, with suspected interstitial lung disease; bronchoalveolar lavage specimens were all negative for pathogens and he had no amelioration from antimicrobial therapy, whereas he rapidly recovered after high-dose steroid therapy.

Even though extrahaematological toxicities were prevalent in the ABVD arm (8 vs. 5), the difference was not statistically significant ($P = 0{\cdot}273$).

With regard to secondary malignancies, 3 patients (11%) in the ABVD arm developed lung cancer, breast cancer and gastric adenocarcinoma, while 2 patients (7%) in the VEPEMB arm developed myelodysplastic syndrome and a soft-tissue sarcoma.

Occurrence of early grade 3–5 and late toxicities are shown in detail in Table V.

Discussion

Even though modest improvements have been achieved for HL in recent years, the outcome of elderly patients with HL

Table V. Toxicity grade ≥3 by treatment.

	ABVD (*N*)	VEPEMB (*N*)	Total (*N*)
Haematological adverse event			
Grade 3	1	1	2
Grade 4	1	3	4
Cardiac adverse event			
Grade 3	2	–	2
Grade 5 (TRM)	1	–	1
Pulmonary adverse events			
Grade 3	1	–	1
Grade 4	1	1	2
Grade 5 (TRM)	–	1	1
Fever (only grade 3)	2	–	2
Mucosite (grade 4)	1	–	1
Cellulitis (grade 4)	–	1	1
Gastrointestinal adverse event	–	1	1
Secondary Neoplasm*	3	2	5

ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; VEPEMB, vinblastine, cyclophosphamide, procarbazine, prednisone, etoposide, mitoxantrone, bleomycin; TRM, treatment-related mortality.
*Secondary neoplasm: lung cancer, breast cancer, myelodysplastic syndrome, soft-tissue sarcoma.

still remains unsatisfactory. Recent clinical trials addressing the issue of improving the prognosis of elderly people have not led to convincing results and no standard treatment recommendations currently exist for this population (Evens & Hong, 2013).

The first challenging drawback when approaching HL in the elderly is the difficulty to carry out large randomized trials due to the small numbers of available patients. Population-based studies have shown that the proportion of HL patients older than 60 years is approximately 20% of the total of HL cases (Stark *et al*, 2002), but this could be even lower, as many cases of HL were actually reclassified as non Hodgkin lymphoma (Miller *et al*, 2002; Klimm *et al*, 2007). Definitely, the incidence of HL in the older population is considerably low.

Pertaining to our randomized trial, despite a four-year recruitment period in 10 participating centres, enrolment was closed in 2006 with a lower number of patients than initially planned. The low accrual rate, in addition to the low incidence of HL in the elderly, was probably related to the fact that the study was limited to non-frail patients and particularly to the evidence that patients older than 65 years frequently present comorbidities that cause physicians not to enrol them in randomized studies.

In the elderly it is important to identify a treatment approach that ensures adequate efficacy and acceptable toxicity. The results of the ABVD regimen, which is still considered the standard in the younger population, are less satisfactory in patients older than 65 years, especially in those with advanced stage disease. The German Hodgkin Study Group (GHSG) recently reported CR rates up to 90% in early stage disease (Boll *et al*, 2013), but for advanced stage patients the efficacy of ABVD was lower, with CR rates ranging between 45% and 65% (Proctor *et al*, 2011; Evens *et al*, 2013).

In the GHSG HD9 study, the BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone) baseline regimen showed good tumour control (freedom from treatment failure of 74%) when applied to patients older than 60 years, but this result was counterbalanced by a 21% toxic death rate (Ballova *et al*, 2005), which was slightly improved when etoposide was omitted from the chemotherapy schedule in a later phase 2 study (Halbsguth *et al*, 2010).

VEPEMB, an originally low aggressive regimen devised for elderly patients, was well tolerated and effective in both early and advanced stage patients. In early stage patients, three courses of VEPEMB followed by involved field radiotherapy obtained excellent results, while in advanced stage patients we obtained a CR rate of 58% and a 5-year FFS rate of 34%, with a low TRM (3%) (Levis *et al*, 2004). The good performance of the VEPEMB regimen has been confirmed in an independent English prospective study (Proctor *et al*, 2012).

On the basis of the previously encouraging results obtained with VEPEMB by the Italian and English study groups (Levis *et al*, 2004; Proctor *et al*, 2012), we launched a randomized study in order to determine if a low aggressive regimen could be superior to the standard ABVD in patients older than 65 years, who were considered fit according to an initial comprehensive geriatric evaluation.

In the present trial we confirmed the safety of both regimens in this subgroup of non-frail patients; in particular, the ABVD results compare very favourably with the toxicity data reported in our early retrospective analysis (Levis *et al*, 1994) and are better than more recent results observed by other study groups, in which a TRM up to 9% was reported for ABVD (Boll *et al*, 2013; Evens *et al*, 2013).

In terms of efficacy, the VEPEMB regimen showed worse PFS and OS than standard ABVD. As a matter of fact, the major finding that emerged from this trial was the superiority, even though not statistically significant, of the standard ABVD regimen. These results are very similar to the OS rates recently reported by other study groups with different regimens (Böll *et al*, 2011; Evens & Hong, 2013). Bleomycin toxicity was lower than expected in this group of elderly patients. We had only one case of BLT, who was assigned to the cohort of patients with advanced disease treated with 6 cycles of ABVD, but the limited number of patients at higher risk of lung toxicity could explain the occasional low rate of BLT. BLT occurred in 15–20% of patients in retrospective studies in elderly HL patients treated with ABVD, but it is not associated with the VEPEMB scheme (Levis *et al*, 2004; Proctor *et al*, 2012).

One possible explanation of the apparent low efficacy of VEPEMB could be the absence of doxorubicin. It is likely

that the low toxicity of doxorubicin-free regimens is counterbalanced by a low efficacy (Weeks *et al*, 2002), whereas in the ABVD, and even more in the PVAG regimen (Böll *et al*, 2011), the inclusion of doxorubicin could bring a significant benefit in terms of efficacy also to older patients.

Unfortunately, the present study failed to achieve the minimum sample size needed to detect any clinically meaningful differences between the two treatment arms. Consequently, these inconclusive findings are probably due to the lack of sufficient statistical power to detect such a difference. Nevertheless, we decided to report the findings of this underpowered study because it may prevent publication bias and our results could be incorporated into future revisions and meta-analyses.

However, our randomized trial supports the general opinion regarding the improved survival of older HL patients in the modern era over recent decades. This is demonstrated by the survival rates observed with ABVD in particular, which nowadays are considerably higher than those observed in retrospective studies of 20 years ago (Mir *et al*, 1993; Levis *et al*, 1994). The better toxicity profile and better survival documented for ABVD in our study could be partly due to the enhanced supportive care measures in the contemporary era, but also to the adoption of more stringent inclusion criteria, based on a thorough assessment and exclusion of frail patients.

Our previous phase 2 study (Levis *et al*, 2004) highlighted the clinical importance of comorbid conditions as a prognostic negative factor for elderly patients, more than age itself. In a recent analysis of prognostic factors in elderly, Evens *et al* (2012) found that age over 70 years and reduction of the ADL score were associated with inferior outcome, thus emphasizing the critical impact of functional status in the prognosis of elderly HL patients. Furthermore, the Study for Hodgkin In the Elderly Lymphoma Database (SHIELD) reported a strong association between the comorbidity scale used and the outcome (Proctor *et al*, 2012).

A distinguishing feature of our trial was the baseline objective selection of the individual patients according to frailty. Several geriatric assessments are available today; we selected the CIRS, ADL and GDS. Age and the above mentioned geriatric scores were useful to exclude the elderly frail population from the analysis, because only patients fulfilling the eligible criteria were enrolled by the centralized office in Alessandria. By excluding the frail population, we reported a low number of early toxic deaths and a satisfactory long-term disease; according to the relatively low accrual, we couldn't identify any difference on the outcome only on the basis of the geriatric scores.

Given the results observed in our randomized trial, we can confirm that the VEPEMB regimen is characterized by an acceptable toxicity profile but with a moderate efficacy; on the other hand ABVD remains a valuable, probably better, approach. Therefore, even if the sample size, and consequently the power of the study, is limited by the low enrolment, the trial is able to provide important information in determining the standard treatment strategy for elderly non-frail HL patients, and can be considered as a platform to design future clinical trials specific for this patient population.

In particular, recent novel promising agents have been identified in the treatment of HL and they should be integrated into the first-line treatment of elderly patients. Brentuximab vedotin has shown encouraging results as monotherapy in heavily pretreated patients and after failure of autologous stem cell transplant (ASCT), with overall response rates ranging between 50% and 75% (Younes *et al*, 2012). These results have led to accelerated approval by the US Food and Drug Administration for patients with either primary refractory HL or those whose disease relapses after ASCT. Moreover, bendamustine has shown a very good toxicity profile in phase II studies in relapsed/refractory HL patients and has been associated with promising activity after failure of multiple lines of treatment (Corazzelli *et al*, 2013; Moskowitz *et al*, 2013). Given the demonstration of a substantial activity associated with a low toxicity profile, these anticancer compounds are currently undergoing clinical trials in the elderly and a direct comparison with the ABVD regimen would be very interesting.

Acknowledgments

The centres that participated in this trial are listed in Appendix 1.

Author contributions

A.L. designed the research and wrote the paper; F.Z., G.C. and A.L. wrote the paper; S.T., M.B., A.B. performed the research; C.M., G.C., S.T. analysed data. F.M., F.I., C.S., A.M.L., D.M., U.V., E.A., D.R.S., D.V., F.S. performed the research.

Appendix I

List of participating centres

1 Alessandria: Francesco Zallio, Stefania Tamiazzo, Flavia Salvi, Alessandro Levis. Haematology Department, SS Antonio & Biagio and C.Arrigo Hospital, Alessandria Italy.
2 Bari: Attilio Guarini. Haematology Unit, National Cancer Research Centre, Istituto Tumori 'Giovanni Paolo II', Bari, Italy.
3 Cagliari: Emanuele Angelucci. Haematology Division, Businco Hospital Cagliari, Italy.
4 Candiolo: Delia Rota Scalabrini. Division of Candiolo Cancer Institute, IRCCS University of Torino Medical School, Candiolo, Italy.
5 Carpi: Katia Cagossi. Unit of Internal Medicine Oncology Ospedale Ramazzini Di Carpi.

6 Catanzaro: Stefano Molica. Department of Onco-haematology, AO of Catanzaro Pugliese-Ciaccio, Italy.
7 Cuneo: Andrea Gallamini. Division of Haematology, Santa Croce e Carle Hospital, Cuneo, Italy.
8 Lecce: Nicola Di Renzo. Division of Haematology Ospedale Vito Fazzi, Lecce, Italy.
9 Lodi: De Fazio Pasqualina. Department of Medical Oncology, AO della provincia di Lodi, Italy.
10 Messina: Donato Mannina. Division of Haematology Papardo Hospital Messina, Italy.
11 Modena: Monica Bellei, Alessia Bari. Department of Diagnostic, Clinical and Public Health Medicine, University of Modena and Reggio Emilia, Modena, Italy.
12 Novara: Gianluca Gaidano. Division of Haematology, Department of Translational Medicine, Amedeo Avogadro University of Eastern Piedmont, Novara, Italy.
13 Palermo: Maurizio Musso. Unit of Onco-haematology and Stem Cell Transplant, Dip. Oncologico La Maddalena, Palermo, Italy.
14 Pavia: Vittorio Fregoni. U.O. di Oncologia Medica I, IRCCS, Fondazione Salvatore Maugeri, Pavia, Italy.
15 Perugia: Anna Marina Liberati. Department Of Surgery And Biomedicine, Division of Oncohaematology with Autologous Transplant, University Of Perugia, Perugia, Italy.
16 Piacenza: Daniele Vallisa. Oncology and Haematology Department, Azienda Unità Sanitaria Locale, Piacenza, Italy.
17 Reggio Calabria: Caterina Stelitano. Haematology Azienda Ospedaliera BMM, Reggio Calabria, Italy.
18 Reggio Emilia: Francesco Merli, Fiorella Ilariucci. Haematology, Arcispedale Santa Maria Nuova-IRCCS, Reggio Emilia, Italy.
19 Sassuolo: Giovanni Partesotti. Division of Oncology, Ospedale di Sassuolo, Sassuolo, Italy.
20 Sondalo: Alessandro Pastorini. Division of Clinical Oncology, AO of Valtellina and Valchiavenna, Sondalo, Italy.
21 Torino: Umberto Vitolo. Haematology, Azienda Ospedaliero Universitaria Città della Salute e della Scienza di Torino, Torino, Italy.
22 Torino: Chiara Monagheddu. Unity of Clinical Epidemiology AO-Universitaria Città della Salute e della Scienza di Torino and CPO Piemonte, Torino, Italy.

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