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ABVD plus radiotherapy versus EVE plus radiotherapy in unfavorable stage IA and IIA Hodgkin's lymphoma: results from an Intergruppo Italiano Linfomi randomized study

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Background: In 1997, the Intergruppo Italiano Linfomi started a randomized trial to evaluate, in unfavorable stage IA and IIA Hodgkin's lymphoma (HL) patients, the efficacy and toxicity of the low toxic epirubicin, vinblastine and etoposide (EVE) regimen followed by involved field radiotherapy in comparison to the gold standard doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) regimen followed by the same radiotherapy program.
Patients and methods: Patients should be younger than 65 years with unfavorable stage IA and IIA HL (i.e. stage IA or IIA with bulky disease and/or subdiaphragmatic disease, erythrocyte sedimentation rate higher than 40, extranodal (E) involvement, hilar involvement and more than three involved lymph node areas).
Results: Ninety-two patients were allocated to the ABVD arm and 89 to the EVE arm. Complete remission (CR) rates at the end of treatment program [chemotherapy (CT) + RT] were 93% and 92% for ABVD and EVE arms, respectively (P = NS). The 5-year relapse-free survival (RFS) rate was 95% for ABVD and 78% for EVE ($P < 0.05$). As a consequence of the different relapse rate, the 5-year failure-free survival (FFS) rate was significantly better for ABVD (90%) than for EVE (73%) arm ($P < 0.05$). No differences in terms of overall survival (OS) were observed for the two study arms.
Conclusions: In unfavorable stage IA and IIA HL patients, no differences were observed between ABVD and EVE arms in terms of CR rate and OS. EVE CT, however, was significantly worse than ABVD in terms of RFS and FFS and cannot be recommended as intial treatment for HL.
Key words: ABVD-EVE, early stage unfavorable Hodgkin lymphoma, radiotherapy

introduction

Many prognostic factors that negatively affect relapse-free survival (RFS) in stage IA and IIA Hodgkin's lymphoma (HL) have been reported before the design of our study [1–8]. Among them, the most important are the presence of bulky disease [1], hilar involvement [6], high erythrocyte sedimentation rate (ESR) [3], a number of involved nodal areas higher than three [4], infradiaphragmatic presentation [2–4, 9] and extranodal (E) lesions [4]. Favorable results have been reported by many authors with the association of a limited number of courses of chemotherapy, mainly doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) [10], followed by different approaches of radiotherapy [11–15].

In particular, concerning the optimal radiation therapy in early-stage HL treated with combined modality approach, some clinical trials clearly showed that a radiotherapy volume size reduction from extended field (EF-RT) to involved field (IF-RT) produces similar results and less toxicity [13, 14, 16].

Some concerns, however, arise about ABVD-based strategies as a consequence of potential pulmonary and cardiac late toxicity, mainly when ABVD is associated to mediastinal irradiation [17–21]. Moreover, the real benefit of bleomycin and dacarbazine remain under discussion.

In 1995, the Cancer and Leukemia Group B (CALGB) reported, in patients failing to combination chemotherapy with mechlorethamine, vincristine, procarbazine and prednisone (MOPP), good results with the salvage epirubicin,

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vinblastine and etoposide (EVE) chemotherapy regimen on the basis of the association of etoposide, doxorubicin and vinblastine [22]. In forty-five relapsing or refractory patients, EVE chemotherapy showed an overall response rate of 73% with 40% complete remission (CR). A pilot study conducted in a small group of patients with localized HL indicated that the strategy of three courses of EVE followed by radiotherapy present low toxicity, but it is associated to a high relapse rate [15]. No randomized multicenter experiences, however, have been so far published comparing, in unfavorable stage IA and IIA, the standard association of ABVD plus radiotherapy to the association of a less intensive and possibly less toxic program-like EVE or an EVE-derived regimen with the same radiotherapy program. EVE regimen was on the basis of the experience of Al-Ismail et al. [23], who describe the potential less cardiac toxicity changing doxorubicin with epirubicin in patients with non-HL. Patients receiving epirubicin tolerated higher dose per course and higher total cumulative dose with less evidence of compromised left ventricular function than patients receiving doxorubicin with no differences in survival and response rates. Lahtinen et al. [24] monitored cardiac toxicity of 24 lymphoma patients, randomized into two multidrug regimens including either epirubicin or doxorubicin; they showed that left ventricular ejection fraction decreased significantly more in the doxorubicin than in the epirubicin group ($P < 0.005$).

In the attempt to verify the efficacy of a regimen potentially less toxic than ABVD, in 1997 the Intergruppo Italiano Linfomi (IIL) started a cooperative randomized study. The aim of the study was to compare, in unfavorable stage IA and IIA, efficacy and toxicity of four courses of ABVD plus IF-RT versus four courses of EVE (a low aggressive modified EVE regimen) plus IF-RT.

patients and methods

study design and patients eligibility

To be included in the study, patients should have a histological confirmed diagnosis of HL. Patients should also be younger than 65 years and should not have received previous treatment for lymphoma or for any other cancer.

Staging procedures included a complete blood count and chemical panel, thoracic and abdominal computed tomography (CT) scan and bone marrow biopsy. On completion of staging assessment, patients in stage IA or IIA were to be considered as unfavorable according to the presence of at least one of the following clinical features: (i) bulky disease defined as a mass of >10 cm or a mediastinal mass of >0.33 of the thoracic diameter; (ii) involvement of more than three nodal areas; (iii) ESR higher than 40; (iv) E involvement; (v) hilar involvement and (vi) infradiaphragmatic presentation. Finally, patients should result negative for HIV infection and should have signed an informed consent to the study.

chemotherapy

All registered and eligible patients were centrally randomized in a 1 : 1 fashion to receive either four cycles of ABVD or four cycles of the EVE regimens. The EVE regimen was scheduled as follows: epirubicin i.v. 70 mg/m^2 on day 1, vinblastine i.v. 6 mg/m^2 on day 1, etoposide i.v. 100 mg/m^2 on day 1, followed by etoposide os 150 mg/m^2 on days 2 and 3. Each course was repeated every 21 days. ABVD regimen was scheduled as first described by Bonadonna et al. [10]: doxorubicin i.v. 25 mg/m^2, bleomycin i.v. 10 U/m^2, vinblastine i.v. 6 mg/m^2 and dacarbazine i.v. 375 mg/m^2. All drugs were delivered on days 1 and 15 every 4 weeks.

radiotherapy

After four cycles of the assigned treatment arm, all patients had to undergo IF-RT on all sites of disease documented before the start of treatment. Radiotherapy should be started 4 weeks after the last cycle of chemotherapy and after complete restaging was achieved. Radiotherapy was initiated only in those patients who received protocol chemotherapy, had sufficient hematopoietic reserves and did not show progressive disease after the end of chemotherapy. Irradiation was administered to all initially involved sites. Total dose to previously involved areas was 36 Gy, given in 20 daily fractions, 5 days/week, using 6–18 MV linear accelerator; X-rays energy, dose prescription and technique of irradiation (parallel opposed fields and direct field) varied according to disease's presentation. Target volumes were defined on the basis of postchemotherapy volume and delineation was obtained on standard simulator X-ray, using personalized shields in all patients with more than one site to be treated. Subcarinal blocks for heart shielding were never used. Irradiation was to be administered to all initially involved regions with one single field, whenever possible.

response assessment and follow-up evaluation

All study data were managed and analysed on an intent-to-treat basis and reported according to the revised Consolidated Standards of Reporting Trials statement for reporting clinical trial results [25]. All patients had physical examination and blood cell count before each chemotherapy course. Response was evaluated at the end of the four courses of both chemotherapy regimens and after completion of the whole program at least 1 month after the end of radiotherapy. Response assessment was carried out according to Cotswolds criteria and it was on the basis of the repetition of a blood count, chemical panel and thoracic and abdominal CT scan. For the evaluation of residual disease, mainly for mediastinum, Ga-67 scan was carried out when necessary. In patients in clinical CR, follow-up examinations were repeated every 6 months for the first 2 years and once a year thereafter.

The actual dose intensity of each drug after four courses of chemotherapy was calculated as mg/m^2/week according to the method of Hryniuk [26]. The relative drug dose intensities of each drug were calculated as the ratio between actual and projected dose intensity.

Survival analysis included overall survival (OS), failure-free survival (FFS) and RFS. All randomized patients were evaluated for OS and FFS analysis; OS was calculated from the date of randomization to the date of death or the last visit; FFS was calculated from the date of randomization to the date of treatment failure, disease relapse or progression, death or the last visit. RFS was calculated only for patients achieving a CR from the date of treatment end to the date of relapse or last visit.

statistical methods

The statistical analyses were carried out by the Statistics and Data Management Unit at the IIL data center using version 10 of the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL). Proportions were compared by means of Fisher's exact test, and all time-to-event distributions were calculated using the Kaplan–Meier method and compared using the log-rank test. For each group comparison, a P value of 0.05 (two-sided) was considered significant. Multivariate analyses of prognostic factors were carried out according to the Cox proportional hazards regression models.

The sample size was calculated on the basis of a noninferiority one-sided test, considering FFS as the primary end point. The study was required to confirm noninferiority for the experimental arm (EVE) if the difference in terms of 3-year FFS was within 15%, assuming a 3-year FFS of 80% for the standard group (ABVD). With a power of 80% and

a significance level of 0.05 using a one-sided test, 84 patients per arm were required. Assuming a 10% rate of ineligible patients after randomization for any reason, a final accrual of 188 patients was planned.

results

From January 1997 to December 2001, 189 patients with HL were registered in the study and randomized. After randomization, eight patients were excluded from study (seven in the ABVD and one in the EVE arm). Six patients (five ABVD and one EVE) were excluded from the study due to incomplete data on staging, treatment and response. One more patient assigned to ABVD retired his consent to continue the treatment program after the first course of chemotherapy. Finally, one patient (ABVD) was lost to follow-up after the second course because he moved to another country. Therefore, 181 eligible patients, for whom response and toxicity data are available, are the object of the present analysis: 92 were randomized to ABVD and 89 to EVE arm; Figure 1.

Median age was 51 years (19–65), and 78 patients were male and 103 female. The adverse prognostic factors that induced to classify our group of patients as unfavorable were distributed as follows: ESR higher than 40 in 91 patients (52%), bulky disease in 49 patients (26%), E involvement in 26 patients (14%), hilar involvement in 27 patients (15%) and infradiaphragmatic presentation in 25 (14%) patients. More than one unfavorable prognostic factor was present in 37 patients (24%). Moreover, an elevated lactate dehydrogenase (LDH) was evident in 22 patients (12%) and a histology subtype other than nodular sclerosis in 54 patients (30%). The International Prognostic Score (IPS) index score [27] was calculated on 154 patients and a value higher than 2 was evident in only 5 patients: 1 allocated to the ABVD and 4 in the EVE arm. Clinical and laboratory features at diagnosis were well balanced between the two treatment arms, as shown in Table 1.

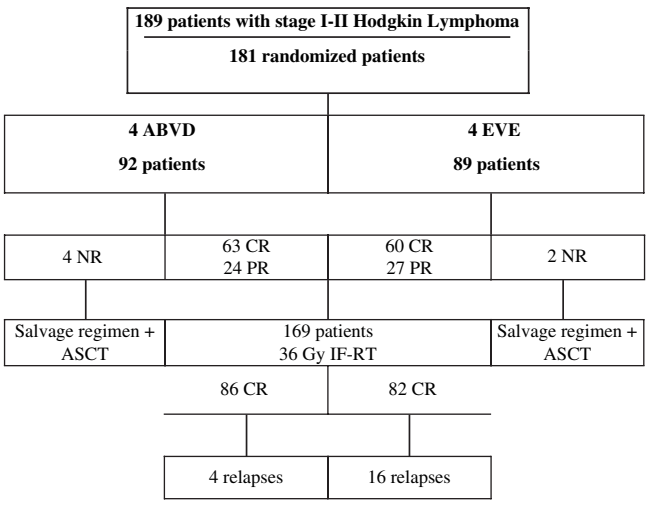

Figure 1. Study schema of the randomized trial comparing a strategy that includes radiotherapy plus doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) versus radiotherapy plus epirubicin, vinblastine and etoposide (EVE).

The mean relative dose intensities at the end of the four courses of chemotherapy were 0.935 and 0.983 for ABVD and EVE, respectively (P = NS). Median follow-up was 62 months. Eight deaths were observed so far: seven due to progression or relapse of HL, four in the EVE and three in ABVD arm, and one related to pneumonia in the EVE arm after the completion of four courses of chemotherapy.

The response to four courses of chemotherapy was not different between the two arms, as shown in Table 2. A CR was obtained in 63 (68%) and 60 (67%) patients treated with ABVD and EVE, respectively. Nonresponder patients, with a reduction of initial adenopathies <50%, were four (4%) in the ABVD and two (2%) in the EVE arm. These patients were submitted to salvage treatments (radiotherapy in three cases or radiotherapy plus cyclophosphamide, oncovin, procarbazine, and prednisone–ABVD–lomustine, Alkeran, and Vindesine in three cases) plus autologous stem-cell transplantation (ASCT). All but one achieved CR. Progression during chemotherapy was nonevident in any of the two arms. One hundred and sixty-nine patients out of 181 (93%) completed the radiotherapy part according to the protocol guidelines.

The results obtained on completion of the whole program at the end of the subsequent IF-RT are summarized in Table 2.

Table 1. Clinical and laboratory features at diagnosis according to treatment arm

	ABVD	EVE	Total
	n (%)	*n* (%)	*n* (%)
Total	92	89	181
Gender			
Male	42 (46)	36 (40)	78 (43)
Age, median (range)			51 (19–65)
Stage			
IA	8 (9)	5 (6)	13 (7)
IIA	84 (91)	84 (94)	168 (93)
Bulky disease	23 (25)	26 (29)	49 (27)
Performance status (Karnofsky index)			
≤80	13 (14)	16 (18)	29 (16)
Extranodal disease	12 (13)	14 (16)	26 (14)
Infradiaphragmatic disease	14 (16)	12 (13)	26 (14)
ESR ≥40	44 (48)	47 (52)	91 (52)
>3 nodal involved sites	25 (46)	29 (54)	54 (30)
LDH higher than normal	12 (13)	10 (11)	22 (12)
Lymphocytes			
<600/μl or <8%	10 (11)	12 (13)	22 (12)
IPS index			
>2	2 (2)	3 (3)	5 (3)
Histology			
NS	58 (46)	69 (54)	127 (70)
MC	18 (49)	19 (51)	37 (20)
LP	17		17 (10)

ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; EVE, epirubicin, vinblastine and etoposide; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; IPS, International Prognostic Score; NS, nodular sclerosis; MC, mixed cellularity; LP, lymphocyte predominance.

Table 2. Responses after chemotherapy (A) and after chemotherapy plus involved field radiotherapy (B)

	ABVD	EVE	Total
A			
No. of patients	92	89	181
CR + CRu	63 (69%)	60 (68%)	123 (68%)
PR	24 (26%)	27 (30%)	51 (28%)
NR	4 (4%)	2 (2%)	6 (3.5%)
Treatment withdrawn	1 (1%)	–	1 (0.5%)
B			
No. of patients	92	89	181
CR	86 (94%)	82 (92%)	168 (92.5%)
PR	2 (2%)	4 (4%)	6 (3.5%)
NR/PD	3 (3%)	3 (3%)	6 (3.5%)
Treatment withdrawn	1 (1%)	–	1 (0.5%)

ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; EVE, epirubicin, vinblastine and etoposide; CR, complete remission; CRu, complete remission probable; PR, partial remission; NR, no response; PD, progressive disease.

No statistical difference was seen in terms of final CR rate: 93% (86 patients) and 92% (82 patients) in the ABVD and EVE arms, respectively. Induction failures were observed in 13 patients: 6 response less than CR (2 in the ABVD and 4 in the EVE arm); 4 nonresponses equally distributed between the 2 arms; 2 progressions (1 in the ABVD and 1 in the EVE arm) and 1 treatment interruption due to toxicity in the ABVD arm.

Relapses have been observed so far in 20 cases: 4 in the ABVD and 16 in the EVE arm ($P = 0.004$).

Five relapses (20%) occurred in the previous IF-RT.

The actuarial 5-year RFS rate of patients entering CR was significantly lower for the EVE (78%) than for the ABVD arm (95%) ($P = 0.002$). As a consequence of the different relapse rate, the 5-year FFS rates were better for the ABVD (90%) than for the EVE arm (73%) ($P = 0.005$), as shown in Figure 2.

Information on toxicity is available on 173 patients. Both regimens were well tolerated and no differences were evident between the two groups in terms of acute hematological and extra-hematological toxicity as shown in Table 3. No cases of toxicity higher than World Health Organization (WHO) grade 2 were seen in terms of lung, heart, kidney, central nervous system and skin except one case of WHO grade 3–4 infection and one case of cardiac toxicity in ABVD arm. One patient died for pneumonia after the completion of chemotherapy, while no other grade 3–4 extra-hematological toxicity were seen in the EVE arm. No evidence of secondary solid tumor or myelodisplastic syndrome has been so far documented.

Most failing and relapsing patients entered a salvage program mainly with high-dose chemotherapy supported by ASCT. Complete response to salvage therapy was reported in 61% of the total of this group. Five-year OS rate was not statistically different between the two arms: 95% for ABVD and 92% for EVE, as shown in Figure 3.

In univariate analysis, IPS, LDH above normal values and type of chemotherapy affected FFS. In multivariate analysis, the independent unfavorable value of EVE regimen was confirmed when LDH and IPS score were preliminary forced into the Cox model ($P = 0.002$)

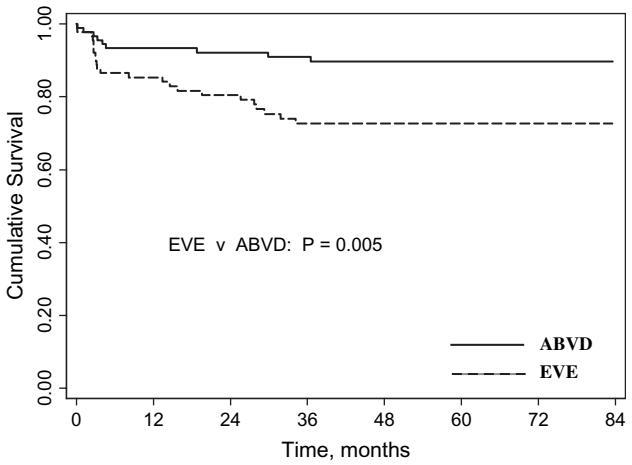

Figure 2. Comparison of failure-free survival between doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) and epirubicin, vinblastine and etoposide (EVE).

Table 3. Grade 3–4 treatment-related toxic effects

	WHO	ABVD *n* (%)	EVE *n* (%)	Total *n* (%)
Anemia	3–4	–	2 (2)	2 (1)
Leucopenia	3–4	13 (14)	13 (15)	26 (14)
Cardiac toxicity	3–4	1 (1)	–	1 (1)
Infections	3–4	1 (1)	1 (1)	2 (1)

WHO, World Health Organization; ABVD, doxorubicin, bleomycin, vinblastine and dacarbazine; EVE, epirubicin, vinblastine and etoposide.

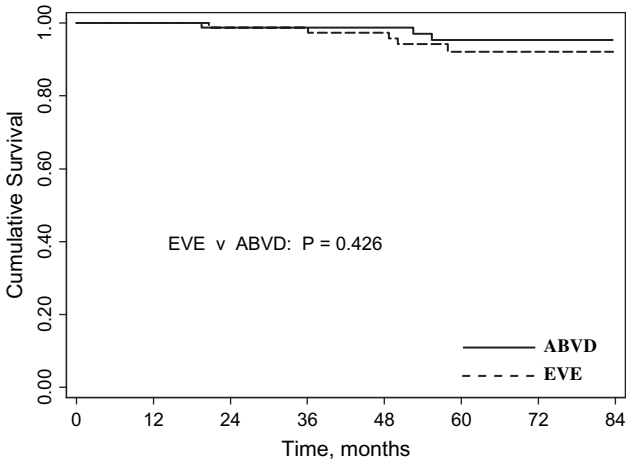

Figure 3. Comparison of overall survival between doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) and epirubicin, vinblastine and etoposide (EVE).

discussion

The optimal treatment of unfavorable stage I and II HL still remains controversial [10–22, 28–31]. The most useful

approach consists of three or four courses of ABVD followed by radiotherapy that has been reported to obtain excellent results in terms of disease control. The major problems of this type of combined modality approach are the long-term cardiac and pulmonary toxic effects, related to the association of radiotherapy with bleomycin and doxorubicin, and secondary solid tumors [32–41]. In order to search for a better balance between efficacy to achieve a long-term cure rate and a reduction of the risk of toxicity, new strategies based either on chemotherapies other than ABVD or on reduction of radiotherapy have been considered [16, 21, 29–31].

There are several trials from literature supporting the ability of IF-RT, consisting in irradiation limited only to the involved sites at diagnosis, to obtain clinical results as good as those achieved with more traditional EF-RT, when IF-RT is given after a limited number of ABVD-based chemotherapy program [14, 20, 29, 30].

Concerning less toxic chemotherapy, in 1995 the CALGB published a salvage study with EVE, a regimen on the basis of etoposide, vinblastine and doxorubicin alternative to ABVD, in patients who were refractory to MOPP [22]. Authors demonstrated that EVE was an effective and low toxic salvage regimen and it was proposed as a substitution of ABVD at least in settings in which compromised lung function may preclude the use of bleomycin. Briezel et al. [21] in 1994 presented the results of the association of six courses of EVE and low dose (15–25 Gy) IF-RT in a small group of 26 advanced stage patients with unsatisfactory results. The patients, however, presented more advanced disease and unfavorable prognostic features in comparison to our group of patients.

Cannellos et al. [31] in 2003 also pointed upon the efficacy of EVE chemotherapy, also as primary systemic treatment for advanced Hodgkin's disease with a 10-year follow-up.

When the present study was started, no data existed in unfavorable stage IA and IIA comparing ABVD plus conventional dosages IF-RT with a less aggressive chemotherapy approach followed by the same radiotherapy program. Our effort was to compare the ABVD-combined strategy to the potentially less toxic EVE regimen in a randomized multicenter study. Our patients were stratified according to the knowledge available at the time when the study was planned in 1995. Otherwise, further experience limited the unfavorable prognostic prediction of hilar involvement or infradiaphragmatic location of the disease [42, 43]. Even if IPS seems to be a well reproducible model in advanced disease, HL at the moment seems to be necessary to well recognize a reproducible prognostic score for initial stage in order to better asses the treatment strategy for unfavorable stage I or IIA HL. Anyway in our series, infradiaphragmatic presentation represented only 14% of the whole population.

In the current study, four courses of EVE obtained the same results of four courses of ABVD in terms of CR rate: 67% for EVE versus 68% for ABVD. The addition of IF increased the CR rate to >90% without any significant difference between the two arms: 92% and 93% for EVE and ABVD arms, respectively. Relapses, however, were significantly higher in the EVE than in the ABVD arm as demonstrated by RFS and FFS curves. This indicates that four courses of EVE are inferior to four courses of ABVD to prevent relapses and to control subclinical disease.

These results are in agreement with those reported in 1999 by Wassermann et al. [15] on a similar group of 53 stage I and II patients treated with three courses of EVE followed by subtotal nodal irradiation. In this CALGB nonrandomized phase II study, no pulmonary toxicity has been reported, but relapses were significant higher than those observed in historical controls with three ABVD plus radiotherapy. Therefore, the favorable profile of EVE in terms of extra-hematological toxicity seemed unfavorably balanced by a higher relapse rate. Moreover, progressions occurred mainly outside the radiotherapy fields, in spite of the use of EF-based radiation approach, and authors indicated that EVE chemotherapy was inferior to ABVD for the control of occult disease. The inferiority of EVE in comparison to ABVD to control subclinical disease was confirmed in our data by the high relapse rate, with 80% relapses occurring outside the radiation fields. The relatively high second-line durable remission rate (60%) achieved in relapsing patients with both conventional and high-dose salvage regimens can explain the absence of OS differences, even if a possible difference in OS might need a longer follow-up.

Both treatments were well tolerated with grade 3–4 leucopenia in 14% of both arms. Only one case of grade 3–4 infection and one case of grade 3–4 cardiac heart toxicity were observed in the ABVD arm. One case of death for pneumonia was observed in the EVE arm after completion of four courses of chemotherapy. Acute hematological and infections toxicity profile of EVE regimen was therefore not particularly favorable in comparison to ABVD. No severe acute lung toxicity was reported in the ABVD arm. In spite of the use of etoposide, secondary acute leukemias or myelodysplastic syndromes have not yet reported in the EVE arm, but follow-up period is still limited.

Results from the present study show that EVE is feasible and active in inducing CRs in unfavorable stage IA and IIA HL disease, but the relapse rate is high and ABVD still remains the best treatment option in our opinion. Particular caution is indicated in exploiting in this set of patients treatment strategies less intensive than three or four courses of ABVD followed by IF-RT.

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