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Original Research

ABVD or BEACOPP$_{baseline}$ along with involved-field radiotherapy in early-stage Hodgkin Lymphoma with risk factors: Results of the European Organisation for Research and Treatment of Cancer (EORTC)–Groupe d'Étude des Lymphomes de l'Adulte (GELA) H9-U intergroup randomised trial☆

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Abstract ***Purpose:*** For early-stage Hodgkin lymphoma (HL), optimal chemotherapy regimen and the number of cycles to be delivered remain to settle down. The H9-U trial compared three modalities of chemotherapy followed by involved-field radiotherapy (IFRT) in patients with stage I-II HL and risk factors (NCT00005584).
Patients and methods: Patients aged 15–70 years with untreated supradiaphragmatic HL with at least one risk factor (age $\geq$ 50, involvement of 4–5 nodal areas, mediastinum/thoracic ratio $\geq$ 0.35, erythrocyte sedimentation rate (ESR) $\geq$ 50 without B-symptoms or ESR $\geq$ 30 and B-symptoms) were eligible for the randomised, open label, multicentre, non-inferiority H9-U trial. The limit of non-inferiority was set at 10% for the difference between 5-year event-free survival (EFS) estimates. From October 1998 to September 2002, 808 patients were randomised to receive either the control arm 6-ABVD-IFRT (n = 276), or one of the two experimental arms: 4-ABVD-IFRT (n = 277) or 4-BEACOPP$_{baseline}$-IFRT (n = 255).
Results: Results in the 4-ABVD-IFRT (5-year EFS, 85.9%) and the 4-BEACOPP$_{baseline}$-IFRT (5-year EFS, 88.8%) were not inferior to 6-ABVD-IFRT (5-year EFS, 89.9%): difference of 4.0% (90%CI, -0.7%–8.8%) and of 1.1% (90%CI,-3.5%–5.6%) respectively. The 5-year overall survival estimates were 94%, 93%, and 93%, respectively. Patients treated with combined modality treatment chemotherapeutic regimen comprising doxorubicin (Adriamycin), bleomycin, vincristine (Oncovin), cyclophosphamide, procarbazine, etoposide and prednisone (BEACOPP)$_{baseline}$ more often developed serious adverse events requiring supportive measures and hospitalisation compared with patients receiving the chemotherapeutic regimen comprising doxorubicin (Adriamycin), bleomycin, vinblastine and dacarbazine (ABVD).
Conclusions: The trial demonstrates that 4-ABVD followed by IFRT yields high disease control in patients with early-stage HL and risk factors responding to chemotherapy. Although non-inferior in terms of efficacy, four cycles of BEACOPP$_{baseline}$ were more toxic than four or six cycles of ABVD.

1. Introduction

In late 1990s, combined modality has become the standard of care for patients with stages I-II supradiaphragmatic Hodgkin lymphoma (HL) and risk factors [1,2]. The risk-to-benefit ratio of therapy has remained a major challenge for physicians and patients. The European Organisation for Research and Treatment of Cancer (EORTC) Lymphoma Group has investigated several risk-adapted strategies to

distinguish between patient subgroups who might benefit from different approaches. Risk factors used in previous trials were applied to the H9 trial design [2,3].

To optimise the treatment for stage I-II HL with risk factors, the randomised, open-label, multicentre, non-inferiority H9-U trial compared three chemotherapy modalities followed by involved-field radiotherapy (IFRT). The mechlorethamine, vincristine (Oncovin), procarbazine, prednisone, doxorubicin (Adriamycin), bleomycin, and vinblastine (MOPP-ABV) regimen [4] used in the H8-U trial [2] was replaced by the standard doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine (ABVD) regimen because the former was associated with more toxicity, particularly second malignancies [5]. In the early 1990s, weekly chemotherapy has been developed to improve disease control while shortening treatment duration [6]. The bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), procarbazine, and prednisone (BEACOPP) regimen provided encouraging results [7]. At the point of time when the H9-U trial was initiated, the reference treatment was a combination of six cycles of ABVD and IFRT. It resulted in the comparison of two experimental combined modalities: four cycles of ABVD or $BEACOPP_{baseline}$ followed by IFRT to six cycles of ABVD followed by IFRT. We report on the results of the EORTC-Groupe d'Étude des Lymphomes de l'Adulte (GELA) H9-U trial for stage I-II HL with risk factors.

2. Methods

2.1. Patients

Patients aged 15–70 years with untreated stage I-II supradiaphragmatic classical HL with risk factors (age $\geq$ 50, stage II with 4–5 involved nodal areas, mediastinum/thoracic (M/T) ratio $\geq$ 0.35, no B-symptoms and erythrocyte sedimentation rate (ESR) $\geq$ 50 or B-symptoms and ESR $\geq$30) were eligible for the study (Fig. 1). Inclusion was based on the diagnosis made by local pathologists; the material was reviewed by a panel of pathologists (Appendix). Patients with lymphocyte-predominant nodular HL subtype were not eligible. Exclusion criteria were: concomitant or previous malignancies other than basal skin or *in situ* cervix carcinoma, concomitant other severe illness, or HIV positivity.

Clinical staging included physical examination, complete blood count, ESR after 1 h, chest film with measurement of the M/T ratio [8], thoracic and abdomen computed tomography, and bone marrow biopsy.

The trial was approved by the EORTC Protocol Review Committee and by ethics committees of each participating centre or country according to local laws. All patients gave written informed consent before study entry. The study was registered at NCT00005584 (ClinicalTrials.gov).

2.2. Treatment

Patients were randomly assigned to receive either six or four cycles of ABVD followed by IFRT (6-ABVD-IFRT and 4-ABVD-IFRT), or four cycles of $BEACOPP_{baseline}$ followed by IFRT (4-$BEACOPP_{baseline}$-IFRT). Transient interruption of enrolment in the $BEACOPP_{baseline}$ arm occurred from February to May 2001 in France because of procarbazine shortage and patients were assigned to 6-ABVD-IFRT or 4-ABVD-IFRT. The ABVD regimen was administered every 28 d; the $BEACOPP_{baseline}$ regimen was repeated on day 22 (Table 1). ABVD and $BEACOPP_{baseline}$ regimens dose-intensities were calculated according to the formulation of Hryniuk [9]. Classical IFRT was begun within3–4 weeks after the end of the last chemotherapy cycle. The field borders were defined based on body anatomy (except for mediastinum). Patients were treated mostly through parallel opposed fields. Adjacent clinically negative areas were not irradiated. Patients in complete remission (CR) or unconfirmed CR (CRu) after chemotherapy received 30 Gy; those in partial remission (PR) received 36 Gy (with 4 Gy boost to sites of partial response). All radiotherapy regimens were applied in fractions of 1.75–2.0 Gy, five fractions per week, with all fields treated each day.

2.3. Study design

The objective was to compare the control arm (6-ABVD-IFRT) to the two experimental arms (4-ABVD-IFRT and 4-$BEACOPP_{baseline}$-IFRT). The primary end-point was the 5-year event-free survival rate (time to disease progression during treatment, relapse or death) assuming that 90% or more of all expected events will occur within 5 years since randomisation. Secondary end-points were relapse-free survival (time to relapse after CR/CRu or death), overall survival and incidence of late complications (second cancer, cardiac toxic effects, radiation pneumonitis, radiotherapy- and chemotherapy-related pulmonary dysfunction occurring >12 months after treatment initiation). Event-free, relapse-free and overall survival estimates were calculated from the date of randomisation to the date of the first event, date of the last examination or 31st December 2010. Time to the development of late complication was calculated from the date of randomisation to the date on which the complication was diagnosed.

Response to treatment (CR, CRu, PR, no change) was defined according to Cotswolds recommendations using CT scan assessment [10]. Response was evaluated after chemotherapy and after radiotherapy. Patients with stable or progressive disease after chemotherapy

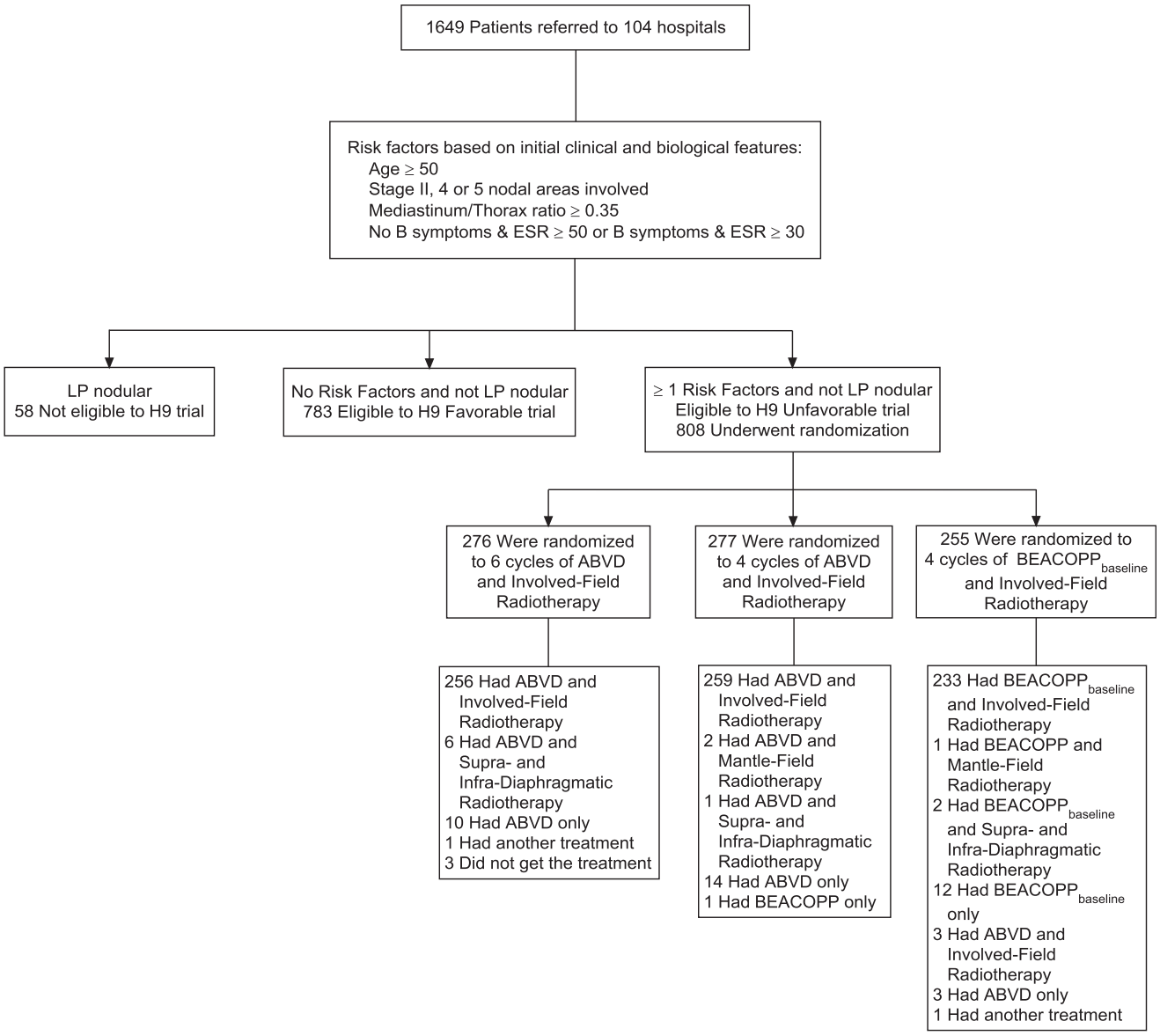


Fig. 1. CONSORT diagram. Study protocol and numbers of patients by treatment arms. enrolment in H9-U trial lasted from October 1998 to September 2002. Transient stoppage of enrolment in the four cycles of $BEACOPP_{baseline}$ and involved-field radiotherapy group occurred from February to May 2001 in France because procarbazine was not available with the conclusion that it probably had no impact on the final results. ABVD denotes doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine. BEACOPP denotes bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), procarbazine, and prednisone. ESR denotes erythrocyte sedimentation rate. MT ratio denotes ratio of the mediastinum to the thorax [9]. Five major lymph node areas were defined as follows: the whole neck including the supraclavicular area (left and right); the axilla including the infraclavicular area (left and right); and the whole mediastinum including the hilar nodes on both sides (one area). LP denotes lymphocyte-predominant histological subtype.

went off protocol. All patients were to be followed at regular intervals after the end of treatment.

Patients were enrolled in 104 hospitals in nine European countries. Registration, randomisation and data collection were performed at the Clinical Research Unit at Centre François Baclesse in Caen, France. Patients were randomised at 1:1:1 ratio for the three arms. randomisation was performed centrally by telephone and stratified by centre with fixed-blocks of six patients. The median follow-up period was 90 months (range, 1–147).

2.4. Statistical analysis

A non-inferiority test was used to compare each of the two experimental arms to the control arm in terms of event-free survival rate at 5 years [11]. The non-inferiority margin was set to 10% in terms of the difference of two rates. Assuming a 5-year event-free survival rate of 90% in the control arm, a minimal sample size of 417 patients were necessary to have 80% power to conclude non-inferiority at a one-sided 5% significance level. The

Table 1
ABVD[a] and BEACOPP$_{baseline}$[b] regimens: doses, schedules of administration and dose-intensity[c] (theoretical and actual).

Regimen		Dose	Administration schedule	Dose-intensity		
				Theoretical weekly dose	Mean actual dose (range)	Mean relative dose-intensity (range)
ABVD	Doxorubicin (Adriamycin)	25 mg/m^2, i.v.	Days 1 and 15	12.5 mg/m^2	11.6 mg/m^2 (1.1–15.4)	93% (9–123)
	Bleomycin	10 mg/m^2, i.v.	Days 1 and 15	5 mg/m^2	4.5 mg/m^2 (1.0–5.8)	91% (19–116)
	Vinblastine	6 mg/m^2, i.v.	Days 1 and 15	3 mg/m^2	2.7 mg/m^2 (0.7–3.5)	91% (23–117)
	Dacarbazine	375 mg/m^2, i.v.	Days 1 and 15	187.5 mg/m^2	172 mg/m^2 (43–223)	92% (23–119)
	Globally, 6 cycles				*95% (43 to 110)*	*91% (35 to 109)*
	Globally, 4 cycles				*96% (25 to 118)*	*92% (23 to 113)*
BEACOPP$_{baseline}$	Bleomycin	10 mg/m^2, i.v.	Day 8	3.3 mg/m^2	3.1 mg/m^2 (0.8–3.8)	93% (24–114)
	Etoposide	100 mg/m^2, i.v.	Days 1–3	100 mg/m^2	92.8 mg/m^2 (0–118)	93% (0–118)
	Doxorubicin (Adriamycin)	25 mg/m^2, i.v.	Day 1	8.3 mg/m^2	8.0 mg/m^2 (5.2–12.3)	96% (63–147)
	Cyclophosphamide	650 mg/m^2, i.v.	Day 1	216.7 mg/m^2	208 mg/m^2 (134–320)	96% (62–148)
	Vincristine (Oncovin)	1.4 mg/m^2, i.v. (absolute dose limited to 2 mg)	Day 8	0.47 mg/m^2 (maxi. 0.67 mg/m^2)	0.34 mg/m^2 (0–0.47)	91% (0–112)
	Procarbazine	100 mg/m^2, p.o.	Days 1–7	233 mg/m^2	206 mg/m^2 (0–298)	88% (0–128)
	Prednisone	40 mg/m^2, p.o.	Days 1–14	187 mg/m^2	168 mg/m^2 (0–237)	90% (0–127)
	Globally				*94% (29 to 109)*	*92% (36 to 115)*

[a] See reference # [4].
[b] See reference # [7].
[c] See reference # [9].

upper bound of the two-sided 90% confidence interval (CI) of the difference (control arm minus experimental arm) was compared with the non-inferiority margin of 10% [11,12]. No interim analysis was planned. A stopping rule was based on the occurrence of: modification of planned treatment, severe treatment-related toxicity within 18 months after randomisation, disease progression, PR after chemoradiotherapy, relapse or early death from any cause. A rate of 20% or more of these occurrences (all events combined) in either arm was considered unacceptable. Stopping rules were based on the binomial distribution of events assessed two years after randomisation [13].

The probabilities of event-free, relapse-free and overall survival and the cumulative probability of late severe complications were estimated with the Kaplan–Meier method. The cumulative probability of a late complication was calculated as 1 minus the probability of survival without the development of that complication. All randomised patients were included in the primary analysis, in the arm they were allocated by randomisation.

3. Results

3.1. Patients

Overall, 808 patients were categorized as having risk factors and enrolled in the H9-U trial from October 1998 to September 2002 (Fig. 1). Protocol violations occurred in 60 (7%) patients and were equally distributed between the three arms. Patient characteristics were well balanced between the three arms (Table 2).

3.2. Treatment delivery

Mean actual dose and relative dose-intensity delivered by chemotherapy regimen are given in Table 1. Overall, 85% of ABVD patients (4 or 6 cycles) and 67% of BEACOPP$_{baseline}$ patients had at least 90% of the target dose. Doxorubicin (Adriamycin) administered exceeded 95% of the target dose in 47%, 57% and 67% of the 6-ABVD-IFRT arm, the 4-ABVD-IFRT arm and the 4-BEACOPP$_{baseline}$-IFRT arm, respectively. Of PR patients after chemotherapy, 71% received 36 Gy with 4 Gy boost according to protocol.

3.3. Response to treatment

After chemotherapy, CR/CRu rate was 68% overall, 75% in the 6-ABVD-IFRT arm, 71% in the 4-ABVD-IFRT arm, and 59% in the 4-BEACOPP$_{baseline}$-IFRT arm (CR/CRu versus others, $P = 0.002$) (Table 3). Among the 221 PR patients after chemotherapy, 134 achieved CR/CRu after radiotherapy (35 patients in the 6-ABVD-IFRT arm, 43 in the 4-ABVD-IFRT arm, 56 in the 4-BEACOPP$_{baseline}$-IFRT arm); 83 patients remained in partial response at the end of treatment and three patients had progressive disease. Information was not available for one patient. At the end of overall treatment, there was no statistically significant difference in response rate (86% CR/CRu rate overall) between the three treatment arms.

3.4. Primary outcome analysis

Progression or relapse occurred in 70 patients; 28 (3.5%) patients had progressive disease during treatment or within 3 months following end of radiotherapy, 15 had early relapse (4–12 months following end of radiotherapy) and 27 had late relapse (of which 25 occurred 13–60 months following end of radiotherapy) (Table 4). Extra nodal disease (20/25 located in thorax) most often concerned progressions and early relapses; they were well balanced between the three treatment arms. The difference between 4-ABVD-IFRT and 6-ABVD-IFRT 5-year event-free survival estimates (85.9% and 89.9%, respectively) was 4.0% (90% CI, 0.7%–8.8%) indicating non-inferiority of 4-ABVD-IFRT relative to 6-ABVD-IFRT. The difference between 4-$BEACOPP_{baseline}$-IFRT and 6-ABVD-IFRT 5-year event-free survival estimates (88.8% and 89.9%, respectively) was 1.1% (90% CI, -3.5%–5.6%) indicating non-inferiority of 4-$BEACOPP_{baseline}$-IFRT relative to 6-ABVD-IFRT (Table 4, Fig. 2).

3.5. Clinical outcome, overall and according to response to treatment

In the overall population, 89 patients developed an event (progression or relapse in 68, death in 21) within five years. Sixty patients had died including 45 who died of disease progression or of treatment-related complication 0–108 months after the end of combined

Table 2
Baseline demographic and clinical characteristics of 808 patients with stage I-I Hodgkin lymphoma and risk factors.*

Demographic or clinical characteristics	Total (N = 808)	6 Cycles of ABVD and involved field radiotherapy (N = 276)	4 Cycles of ABVD and involved field radiotherapy (N = 277)	4 $BEACOPP_{baseline}$ and involved field radiotherapy (N = 255)
Age – yearr				
Median	30.7	30.5	30.2	31.0
Range	15–69	15–69	15–69	15–69
Male:female ratio	0.95:1	1.00:1	0.88:1	0.98:1
B symptoms present – no. (%)	352 (46)	130 (50)	117 (45)	105 (43)
Erythrocyte sedimentation rate				
Median – mm/1st hour	51	52	53	49
Range	1–141	1–141	1–124	1–140
Number of lymph node areas involved – no. (%)				
≤ 3	623 (81)	209 (80)	212 (81)	202 (83)
≥ 4	142 (19)	51 (20)	50 (19)	41 (17)
Mediastinal involvement – no. (%)	658 (86)	227 (87)	220 (84)	211 (86)
Large mediastinal mass[a]	324 (42)	108 (42)	105 (40)	111 (45)
Histological analysis				
Number of patients	538	189	172	177
Type of disease[b] – no. (%)				
Lymphocyte-predominant: nodular	3 (<1)	1 (<1)	2 (1)	0 (0)
diffuse	1 (<1)	0 (0)	0 (0)	1 (1)
Nodular sclerosing	491 (91)	172 (91)	157 (91)	162 (91)
Mixed cellularity	18 (3)	8 (4)	3 (2)	7 (4)
Hodgkin lymphoma of unspecified type	19 (4)	7 (4)	7 (4)	5 (3)
Non-Hodgkin lymphoma	5 (1)	1 (<1)	2 (1)	2 (1)
Not Hodgkin lymphoma	1 (<1)	0 (0)	1 (1)	0 (0)
Overall treatment duration – mo[c]				
Median	6.7	8.4	6.6	5.6
Range	0–16.6	0–14.9	0–16.6	0–11.7
Follow-up duration – mo[d]				
Median	90	91	88	90
Range	1–147	1–147	1–144	1–144

*Because of rounding, percentages may not total 100. ABVD denotes doxorubicin (Adriamycin), bleomycin, and vinblastine; BEACOPP denotes bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), procarbazine, and prednisone.

[a] Large mediastinal mass was defined, in patients with mediastinum involvement, as a ratio of mediastinum to thorax of at least 0.35 at the level of T5 through T6 while the patient was standing.

[b] Histological type after review by the EORTC panel of pathologists (298 cases reviewed of 390, 76%) and the GELA-Pathology (240 cases reviewed of 418, 57%).

[c] The overall duration of treatment was defined as the time from randomisation to the end of radiation course.

[d] The follow-up duration was defined as the time from randomisation to the date of last news or1st January 2011, whichever came first.

Table 3
Response to treatment for 808 patients with stage I-I Hodgkin lymphoma and risk factors.*

	Total (N = 808)	6 Cycles of ABVD and involved field radiotherapy (N = 276)	4 Cycles of ABVD and involved field radiotherapy (N = 277)	4 $BEACOPP_{baseline}$ and involved field radiotherapy (N = 255)
Response at the end of chemotherapy – no. (%)				
Patients with information available[a]	717	244	247	226
Complete remission	203 (28)	82 (34)	71 (29)	50 (22)
Unconfirmed complete remission	287 (40)	99 (41)	104 (42)	84 (37)
Partial remission	221 (31)	59 (24)	71 (29)	91 (40)
Progression	5 (<1)	4 (1)	1 (<1)	0 (0)
Early death	1 (<1)	0 (0)	0 (0)	1 (<1)
Response at the end of treatment – no. (%)				
Patients with information available[b]	730	250	250	230
Complete remission	325 (45)	119 (48)	111 (45)	95 (41)
Unconfirmed complete remission	297 (41)	98 (39)	103 (41)	96 (42)
Partial remission	91 (12)	24 (10)	33 (13)	34 (15)
Progression	15 (2)	8 (3)	3 (1)	4 (2)
Early death	2 (<1)	1 (<1)	0 (0)	1 (<1)

*Because of rounding, percentages may not total 100. ABVD denotes doxorubicin (Adriamycin), bleomycin, and vinblastine; BEACOPP denotes bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), procarbazine, and prednisone; and CI confidence interval.
[a] After chemotherapy, response was not evaluated in 16 patients and the evaluation form not completed in 75 patients.
[b] At the end of chemotherapy and radiotherapy, response was not evaluated in 0 patients and the evaluation form not completed in 78 patients.

Table 4
Events and survival estimates for 808 patients with stage I-I Hodgkin lymphoma and risk factors.*

	Total (N = 808)	6 Cycles of ABVD and involved field radiotherapy (N = 276)	4 Cycles of ABVD and involved field radiotherapy (N = 277)	4 $BEACOPP_{baseline}$ and involved field radiotherapy (N = 255)
Progression/early[a] and late relapse – no. (%)	28/15 + 27 (9)	10/2 + 7 (7)	9/6 + 15 (11)	9/7 + 5 (8)
Site of progression or relapse				
Nodal only, within irradiated field	7/6 + 12 (3)	2/1 + 3 (2)	3/3 + 7 (5)	2/2 + 2 (2)
Nodal only, outside irradiated field	7/3 + 6 (2)	2/0 + 2 (1)	3/1 + 2 (2)	2/2 + 2 (2)
Extra nodal	12/6 + 7 (3)	5/1 + 1 (3)	2/2 + 5 (3)	5/3 + 1 (4)
Unspecified	2/0 + 2 (<1)	1/0 + 1 (1)	1/0 + 1 (1)	0/0 (0)
Duration of response[b] – mo				
Median	88	88	87	89
Range	1–139	8–139	1–136	1–136
CR/CRu patients at end of treatment – no.	622	217	214	191
Early and late relapse – no.	8 + 22	1 + 5	4 + 12	3 + 5
5-Year relapse-free survival – % (95% CI)				
5-Year relapse-free survival – % (95% CI)	95 (93–97)	97 (94–99)	92 (87–95)	96 (92–98)
By mediastinal mass: M/T ratio < 0.35	95 (92–97)	98 (94–100)	93 (86–96)	94 (88–97)
M/T ratio ≥ 0.35	95 (91–97)	95 (87–98)	91 (82–96)	99 (91–100)
PR patients at end of treatment – no.	91	24	33	34
Progression/early and late relapse – no.	14/6 + 4	2/1 + 2	6/2 + 2	6/3 + 0
5-Year progression-free survival – % (95% CI)	75 (64–82)			
5-Year event-free survival – % (95% CI)	88 (86–90)	89.9 (86–93)	85.9 (81–90)	88.8 (84–92)
Difference between groups – (90% CI)				
6 ABVD-IFRT versus 4 ABVD-IFRT		4.0% (0.7%–8.8%)		
6 ABVD-IFRT versus 4 $BEACOPP_{baseline}$-IFRT		1.1% (−3.5%–5.6%)		
Death – no. (%)	60 (7)	18 (7)	21 (8)	21 (8)
Progressive disease	29 (3)	5 (2)	11 (4)	13 (5)
Treatment-related	16 (2)	7 (3)	7 (3)	2 (1)
Not-related to HL	5 (<1)	1 (<1)	1 (<1)	3 (1)
Second cancer	2 (<1)	1 (<1)	0 (0)	1 (<1)
Unspecified cause	8 (1)	4 (1)	2 (1)	2 (1)
5-Year overall survival – % (95% CI)[c]	93 (91–95)	94 (90–96)	93 (89–95)	93 (89–96)
10-Year overall survival – % (95% CI)	91 (88–93)	93 (89–95)	91 (87–94)	89 (83–93)

[a] Progression denotes treatment failure during treatment or within 3 months after treatment completion; early relapse denotes relapse occurring within 4–12 months after treatment completion; late relapse denotes relapse occurring >12 months after treatment completion.
[b] The analysis of duration of response was confined to the 622 patients who had a complete remission (CR) or an unconfirmed complete remission (CRu).
[c] The median follow-up of the patients who survived was 98 months (range, 1–147) in the six cycles of ABVD and IFRT group, 95 months (range, 1–144) in the four cycles of ABVD and IFRT group, and 95 months (range, 1–141) in the four cycles of $BEACOPP_{baseline}$ and IFRT group.

chemoradiotherapy (Table 4). Deaths were well balanced between the three treatment arms leading to 5-year overall survival estimates of 94%, 93% and 93% after 6-ABVD-IFRT, 4-ABVD-IFRT and 4-BEACOPP$_{baseline}$-IFRT, respectively (Table 4, Fig. 3).

The 5-year event-free survival estimate was 93% (95% CI, 90%–95%) for the 490 patients who achieved a CR/CRu after chemotherapy and 84% (95% CI, 79%–88%) in the 221 patients with PR after chemotherapy.

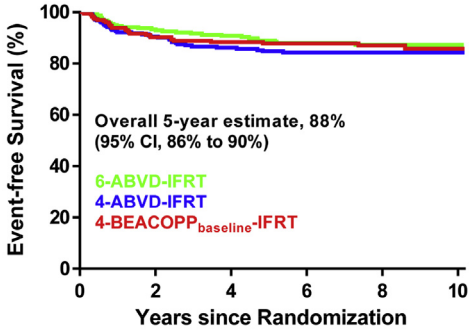
Among the 622 patients who achieved CR/CRu at end of treatment, 30 subsequently relapsed. A higher relapse rate was noticed in patients treated with 4-ABVD-IFRT (5-year relapse-free survival estimate, 92%) compared to 6-ABVD-IFRT (97%) and 4-BEACOPP$_{baseline}$-IFRT (96%). In these 622 patients, the relapse-free survival was independent of response to chemotherapy. The relapse-free survival rates were similar whatever the mediastinal mass (M/T ratio <0.35 versus ≥ 0.35); they were also similar whatever the combined modality treatment assigned. In the 91 patients who achieved a PR at the end of treatment, 24 subsequently failed: 14 progressed within 3 months, six developed early and four developed late relapses (Table 4). Of the remaining 67 patients, one died of treatment-related complication (7 months), one of disease not-related to HL (64 months) and one of unspecified cause (87 months).

3.6. Toxicity of treatment, supportive measures, and late adverse events

Overall, grade 3 or 4 haematological toxicity developed in 74% of patients during chemotherapy (Table 5). Thirteen percent of patients experienced serious adverse events leading to eight chemotherapy-related deaths. While grade 3 or 4 neutropenia and use of growth factors were less frequent after BEACOPP$_{baseline}$, treatment with antibiotics, red-cell transfusions, hospitalisation and serious adverse events were almost double in the BEACOPP$_{baseline}$ arm as compared to the pooled ABVD arms ($P \leq 0.001$ each single test). Grade 3 or 4 infections developed in 3% of patients whatever the treatment arm. During or after radiotherapy, two and 15 patients developed haematological and non-haematological toxicity, respectively. However, stopping rules were not met. Late cardiovascular toxicity was reported in 1% of patients giving a 5-year cumulative estimate of 0.8% (Table 4). Late pulmonary complication was reported in 2% of patients (overall 5-year cumulative estimate, 1.7%). A second malignancy developed in 25 patients 8–118 months after randomisation giving a 5-year cumulative incidence estimate of second cancer of 1.5% (Table 4).

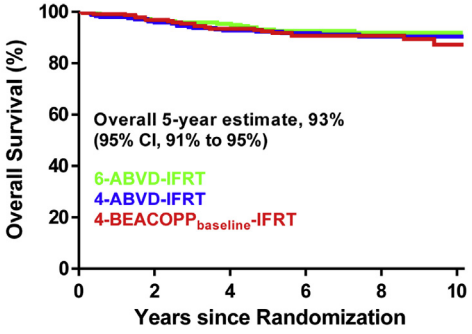
4. Discussion

In patients with early-stage supradiaphragmatic HL and risk factors, the H9-U trial shows non-inferiority of both experimental arms (4-ABVD-IFRT or 4-BEACOPP$_{baseline}$-IFRT) to the reference arm (6-ABVD-IFRT). A combination of four cycles of ABVD and IFRT 30 Gy gives high disease control rate, with progression rate during treatment of 3.5%, and 5-year event-free and overall survival estimates of 86% and 93%, respectively.



Patients at Risk						
6-ABVD-IFRT	276	244	225	185	129	42
4-ABVD-IFRT	277	231	204	174	120	34
4-BEACOPP$_{baseline}$-IFRT	255	218	194	166	113	36

Fig. 2. Kaplan–Meier estimates of event-free survival among patients enrolled into the H9-U trial who were randomly assigned to receive either six cycles of ABVD and involved-field radiotherapy or four cycles of ABVD and involved-field radiotherapy or four cycles of BEACOPP$_{baseline}$ and involved-field radiotherapy. (ABVD denotes doxorubicin (Adriamycin), bleomycin, vinblastine and dacarbazine. BEACOPP denotes bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), procarbazine and prednisone).



Patients at Risk						
6-ABVD-IFRT	276	252	236	195	137	43
4-ABVD-IFRT	277	245	218	188	126	35
4-BEACOPP$_{baseline}$-IFRT	255	233	204	170	117	37

Fig. 3. Kaplan–Meier estimates of overall survival among patients enrolled into the H9-U trial who were randomly assigned to receive either six cycles of ABVD and involved-field radiotherapy or four cycles of ABVD and involved-field radiotherapy or four cycles of BEACOPP$_{baseline}$ and involved-field radiotherapy. (ABVD denotes doxorubicin (Adriamycin), bleomycin, vinblastine and dacarbazine. BEACOPP denotes bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), procarbazine and prednisone).

Table 5
Toxicity of treatment, supportive measures, and late adverse events[a] in 808 patients with stage I–I Hodgkin lymphoma and risk factors.*

Toxicity, treatment effects, and cumulative estimates	Total (N = 808)	6 Cycles of ABVD and involved field radiotherapy (N = 276)	4 Cycles of ABVD and involved field radiotherapy (N = 277)	4 $BEACOPP_{baseline}$ and involved field radiotherapy (N = 255)
Acute grade 3–4 haematological toxicity related to chemotherapy – no. (%)				
Patients with information available	756	256	261	239
At least one toxicity	562 (74)	203 (79)	195 (75)	164 (69)
Anaemia	16 (2)	2 (1)	3 (1)	11 (5)
Thrombocytopenia	5 (1)	1 (<1)	1 (<1)	3 (1)
Neutropenia	346 (46)	136 (53)	131 (50)	79 (33)
Nausea-vomiting	57 (8)	29 (11)	15 (6)	13 (5)
Blood transfusion	32 (4)	6 (2)	5 (2)	21 (9)
Growth factors used	172 (23)	74 (29)	65 (25)	33 (14)
Administration of antibiotics	57 (8)	15 (6)	12 (5)	30 (13)
Hospitalisation	113 (15)	29 (11)	32 (12)	52 (22)
Serious adverse event	95 (13)	22 (9)	27 (10)	46 (19)
Chemotherapy stopped definitively	18 (2)	6 (2)	5 (2)	7 (3)
Acute grade 3–4 toxicity related to radiotherapy – no. (%)				
Patients with information available	717	244	243	230
At least one toxicity	17 (2)	2 (1)	9 (4)	6 (3)
Haematological	2 (<1)	0 (0)	1 (<1)	1 (<1)
Pulmonary	7 (1)	1 (<1)	4 (2)	2 (1)
Mucositis	3 (<1)	0 (0)	3 (1)	0 (0)
Cutaneous	4 (1)	0 (0)	2 (2)	2 (2)
Nausea-vomiting	4 (1)	1 (<1)	1 (<1)	2 (1)
Radiotherapy stopped definitively	1 (<1)	1 (<1)	0 (0)	0 (0)
Late cardiovascular toxicity – no. (%)	9 (1)	5 (2)	4 (1)	0 (0)
Myocardial infarction, angina pectoris	4 (<1)	2 (1)	2 (<1)	0 (0)
Congestive heart failure	1 (<1)	1 (<1)	0 (0)	0 (0)
Constrictive pericarditis	1 (<1)	1 (<1)	0 (0)	0 (0)
Arterial peripheral vasculopathy	3 (<1)	1 (<1)	2 (<1)	0 (0)
5-Year cumulative probability – % (95% CI)	0.8 (0.4–1.9)	0.8 (0.2–3.1)	1.7 (0.6–4.5)	0.0 (–)
10-Year cumulative probability – % (95% CI)	1.4 (0.7–2.7)	2.3 (1.0–5.6)	1.7 (0.6–4.5)	0.0 (–)
Late pulmonary toxicity – no. (%)	13 (2)	2 (1)	7 (3)	4 (2)
Pneumonitis	5 (1)	1 (<1)	2 (1)	2 (1)
Dyspnoea	5 (1)	0 (0)	4 (1)	1 (<1)
Functional test altered	3 (<1)	1 (<1)	1 (<1)	1 (<1)
5-Year cumulative probability – % (95% CI)	1.7 (1.0–2.9)	0.8 (0.2–3.2)	2.5 (1.1–5.5)	1.7 (0.6–4.7)
10-Year cumulative probability – % (95% CI)	1.9 (1.1–0.3.3)	0.8 (0.2–3.2)	3.3 (1.5–6.9)	1.7 (0.6–4.7)
Any second cancer – no. (%)	25 (3)	11 (4)	8 (3)	6 (2)
Type of second cancer – no. (%)				
Acute leukaemia or myelodysplasia[b]	1 (<1)	0 (0)	0 (0)	1 (<1)
Non-Hodgkin lymphoma[c]	1 (<1)	1 (<1)	0 (0)	0 (0)
Solid tumour[d]	23 (3)	10 (4)	8 (3)	5 (2)
5-Year cumulative probability – % (95% CI)	1.5 (0.8–2.7)	1.7 (0.6–4.4)	1.7 (0.7–4.5)	0.9 (0.2–3.7)
10-Year cumulative probability – % (95% CI)	6.1 (3.8–9.7)	8.2 (4.0–16.5)	5.6 (2.5–12.3)	4.3 (1.8–10.1)

*Because of rounding, percentages may not total 100. ABVD denotes doxorubicin (Adriamycin), bleomycin and vinblastine; BEACOPP denotes bleomycin, etoposide, doxorubicin (Adriamycin), cyclophosphamide, vincristine (Oncovin), procarbazine and prednisone; and CI confidence interval.

[a] Late adverse effect denotes toxicity occurring >12 months after treatment completion.

[b] One case of myelodysplasia developed 25 months after randomisation in a 17-year female patient at diagnosis who received salvage treatment with high-dose chemotherapy and autologous stem-cell transplantation.

[c] One complete responder developed a non-Hodgkin lymphoma 51 (58-year male) months after randomisation. In addition, a 35-year female in complete remission after 4-ABVD-IFRT developed a synchronous non-Hodgkin lymphoma eight months after treatment initiation and was excluded from the cumulative analysis.

[d] Of the 23 cases of solid tumours that occurred 12–117 months after randomisation, 12 developed in patients over the age of 50 at diagnosis, 11 within involved irradiated areas (infield) and 12 outside irradiated areas (outfield). There were five infield and five outfield solid tumours in the six cycles of ABVD and IFRT group, three and five in the four cycles of ABVD and IFRT group, and three and two in the four cycles of $BEACOPP_{baseline}$ and IFRT group, respectively.

Comparisons between 4-BEACOPP$_{baseline}$-IFRT and 6-ABVD-IFRT indicate that the two treatments have similar efficacy on event-free and overall survivals. Our results compare well with the 4-BEACOPP$_{baseline}$ and IFRT 30 Gy of the HD11 trial in which the 5-year freedom from treatment failure and the 5-year overall survival estimates were 87% and 94.6%, respectively [14]. In our study, however, the proportion of patients achieving a complete remission is lower after 4-BEACOPP$_{baseline}$ than after 4-ABVD: 59% versus 71%, based on clinical examination and local CT-scan evaluation and without positron-emission tomography (PET). This figure might be the result of lower theoretical dose-intensity and lower mean actual dose of doxorubicin (Adriamycin) with BEACOPP$_{baseline}$ compared with ABVD despite similar mean relative dose-intensity of doxorubicin (Adriamycin) in the two regimens. Moreover, the proportion of patients who developed serious adverse events or who were hospitalised is twofold higher after BEACOPP$_{baseline}$ than after ABVD a finding that confirms the results of the HD11 trial [14]. Altogether, these results suggest that the risk-to-benefit ratio favours the standard ABVD over BEACOPP$_{baseline}$.

Comparisons between 4-ABVD-IFRT and 6-ABVD-IFRT (including IFRT 30 Gy in both) indicate that the two treatments have similar efficacy on event-free and overall survivals. In line with our results, the four cycles of ABVD and IFRT 30 Gy of the HD11 trial is associated with 5-year freedom from treatment failure and 5-year overall survival estimates of 85.3% and 94.3%, respectively [14].

Since the design of the H9 trial, the standard therapy of early stage HL with risk factors and treatment strategies have changed. Based on the results of the HD14 trial in early unfavourable HL, the German Hodgkin Study Group has replaced four cycles of ABVD and IFRT 30Gy by a combination of two cycles of BEACOPP$_{escalated}$ and two cycles of ABVD followed by IFRT 30 Gy that induce significantly higher 5-year freedom from treatment failure rate [15].

Since the design of the H9-U trial, radiotherapy volumes have been reduced from IFRT to involved node or involved site radiotherapy [16–18] and a risk-adapted treatment strategy has been associated with response-adapted therapy using early PET [19,20]. In the EORTC/LYSA/FIL H10 trial in early stages with risk factors, the experimental treatment included two cycles of ABVD followed by in PET positive patients two cycles of BEACOPP$_{escalated}$ and involved-node radiotherapy 30Gy; it was compared to four cycles of ABVD and involved-node radiotherapy 30Gy [18]. In non-bulky stages I-II HL, the RAPID trial showed that patients with negative PET findings after three cycles of ABVD have a good prognosis with or without consolidation radiotherapy [21]. In the current HD17 trial, response after two cycles of BEACOPP$_{escalated}$ and two cycles of ABVD is investigated by PET to identify among patients with intermediate stage of those who can benefit from chemotherapy alone [22]. The use of PET-guided radiotherapy should be considered with caution until the results of these trials are available.

Nowadays, PET plays increasing role in identifying patients at risk of relapse who might benefit from another treatment (including dose-intensified chemotherapy with or without radiotherapy) and those who can be cured with chemotherapy alone. Four cycles of ABVD and IFRT 30Gy have been a reference treatment to develop strategies. It remains an effective option for patients with early-stage HL and risk factors responding to chemotherapy.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2017.05.005.

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