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Radiation therapy compared with chemotherapy for consolidation of chemotherapy-induced remission of advanced Hodgkin lymphoma: a study by the Eastern Co-operative Oncology Group (E1476) with >20 years follow-up

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Abstract

MOPP-Bleo (nitrogen mustard, vincristine, procarbazine, prednisone and bleomycin) induction therapy was given to 253 evaluable patients with Hodgkin lymphoma, stages IIIB, III_s, or IV. Complete response (CR) occurred in 145 patients (57%) and partial response (PR) in 93 (37%). Of those 238 responders, 178 were randomized to consolidation therapy, and 164 were eligible and analyzable, including 114 CRs [55 patients randomized to ABVD and 59 to radiation therapy (RT)] and 50 partial responders (PRs) (25 each randomized to ABVD and RT). Among the 50 patients with PR, 34 (68%) converted to CR (16 with ABVD and 18 with RT). Therefore, of 253 patients, 182(72%) achieved CR and 56 (22%), PR. Median follow-up for all patients is 22.3 years and the estimated overall survival (OS) rate at 20 years is 48%. Of the 148 eligible, analyzable patients with CR, the estimated proportion remaining in CR at 20 years is 62%. OS at 20 years was significantly greater for patients receiving ABVD consolidation (66%) when compared with those who received RT consolidation (43%) ($p = 0.002$). Treatment toxicity was acceptable. After MOPP-Bleo induction for advanced Hodgkin lymphoma, ABVD provides better consolidation than local RT.

Keywords: Hodgkin lymphoma, chemotherapy, radiation therapy, long-term follow-up

Introduction

In the first phase of this study, the efficacy of a MOPP-Bleo regimen devised by the Southwest Oncology Group (SWOG) was tested as induction therapy and the results were compared with historical MOPP controls treated by the Eastern Co-operative Oncology Group (ECOG) [1,2]. In the second phase, those patients who one month after completion of 6 cycles of MOPP-Bleo were in complete (CR) or partial response (PR) were randomly assigned to consolidation therapy with ABVD or RT. The object of this phase was to determine if one of those post-induction therapies was more effective than the other in converting PR to CR, or more effective in maintaining the disease-free and overall survival (OS).

Methods

Patient selection

Patients aged 16–70 years with histologically proven Hodgkin lymphoma and clinical or pathologic stage IIIB, III_s, or IV [3] were eligible for the study. Patients who had prior chemotherapy were ineligible, but prior RT was allowed if the site of relapse was not within the prior RT field. Patients were required to have a white blood cell count (WBC) of $\geq 4000/\mu\text{L}$ and a platelet count of $\geq 100,000/\mu\text{L}$, unless the marrow was infiltrated with Hodgkin lymphoma, or hypersplenism was documented. In those cases, patients were required to have a WBC of $>2000/\mu\text{L}$ and a platelet count $>75,000/\mu\text{L}$. Patients were also required to have a normal renal function (blood

urea nitrogen <25 mg% and serum creatinine ≤ 2.0 mg%) but no exclusions were made for hepatic dysfunction.

Eligibility determination, registration, pathology review, and randomization were performed centrally. Patients entered on induction therapy were stratified according to age (<35 years, ≥ 35 years), performance status (0–1, 2–4), and stage. A total of 301 patients with a median age of 34 years (range, 10–67 years) were registered on study and 253 were analyzed for response and survival, while 48 patients were considered unevaluable. Toxicity was evaluated for all 298 patients who received induction therapy with any cycles of MOPP-Bleo.

Treatment, measurement of effects, and follow-up

Induction therapy consisted of six courses of MOPP-Bleo (Figure 1). Each course consisted of nitrogen mustard, vincristine, procarbazine, and prednisone given in previously reported standard doses and schedule [4], to which intravenous bleomycin, 2 mg/m² [5] was added on days 1 and 8. Cough, dyspnea, dry rales, or pulmonary parenchymal lesions on chest X-ray during bleomycin therapy required discontinuation of bleomycin until the cause of these findings could be ascertained. Chest X-rays were required at least every 6 weeks during bleomycin therapy. Pulmonary function studies were performed before bleomycin therapy and periodically throughout the study. If the FVC or D_{50} fell to 50% or less of pretreatment values, bleomycin was discontinued. The maximum allowed doses of bleomycin and doxorubicin were 36 mg/m² and 150 mg/m², respectively.

Induction therapy was terminated if progressive disease was documented after three cycles of MOPP-Bleo, or if no change occurred in measurable disease after six cycles of therapy.

Patients with CR or PR after induction were randomized to the consolidation step, and RT or ABVD. Treatment began 1 month after completion of induction therapy if the WBC was $\geq 4000/\mu\text{L}$ and

platelet count $\geq 100,000/\mu\text{L}$, or postponed until that level of hematologic recovery occurred.

Radiation was delivered during consolidation to all sites known to be involved with disease prior to induction therapy. In addition, the spleen was irradiated if para-aortic nodal or liver involvement was documented. Para-aortic nodes were also irradiated if both supradiaphragmatic and pelvic nodes were initially involved. The site of the original lymph node biopsy was also routinely irradiated. Radiation was delivered by standard techniques with megavoltage equipment utilizing parallel opposed ports. Shaped fields were employed with blocks individualized for each patient. If radiation was required on both sides of the diaphragm, one side was completed and then after a 2–4 weeks break, the other side was irradiated. The mid-plane total dose was 150–200 Gy given at a rate of 15–20 Gy per fraction, five fractions weekly. Liver and whole lung maximum doses were restricted to 15 Gy. Radiation treatment was interrupted if the WBC count fell below 2000/ μL and/or platelets decreased to $<50,000/\mu\text{L}$, and resumed when counts rose above those levels. Port films were taken weekly. Radiation planning and site mapping were reviewed centrally before initiation of radiotherapy. Sites of residual disease delineated at the end of induction therapy, the treatment plan and isodose distribution, simulation films, beam verification films, and the calculation sheet were all included in this central review.

ABVD was given every 35 days for three cycles with adriamycin, bleomycin, vinblastine, and dacarbazine given in previously reported standard doses and schedules [5].

Patients ≥ 60 years old received 50% of the full dose of myelosuppressive drugs on the first consolidation cycle. If well tolerated, full doses were given in subsequent cycles. Patients randomized to ABVD consolidation received two-thirds of calculated doses for the first course if in the opinion of the investigator cytopenias during induction therapy warranted caution.

Figure 1. Schema for study treatment.

Patients were restaged 1 month after the end of consolidation therapy to document CR. Repeat biopsy of previously involved sites was frequently performed as part of restaging, but positron emission tomography scans were not used. Patients in CR were then followed without further therapy until relapse.

Statistical methods

A CR was defined as complete resolution of all palpable and radiologically demonstrable disease. PR was defined as less than complete resolution of all known disease, but of at least 50% of the sum of the products of the dimensions of all measurable lesions. Patients were observed for remission status and survival every 3 months until progression and patient deaths were reported to the central operations office after confirmation via death certificate.

Disease-free interval (DFI) was defined from the time of randomization to disease recurrence for patients with a CR from induction therapy. For patients with a PR converted to CR during consolidation, DFI was calculated from the time CR was documented. Therefore, DFI comparison of consolidation arms was performed separately for those two groups of patients using eligible and analyzable patients as well as all patients randomized to consolidation in an intent-to-treat analysis. Patients dying without recurrence were censored at the time they were last reported to be disease-free, which was the time of death if they were known not to have recurred before death. Progression-free survival (PFS) was calculated from randomization to relapse or death. Survival was measured from randomization to death from any cause. The Kaplan–Meier method and the Cox proportional hazard regression model were used to estimate failure rates, hazard ratio (HR), and 95% confidence intervals (CI). The log-rank test and its stratified version based on stratification factors (age factor) were used to compare survival-failure distributions. Fisher's exact test and Wilcoxon rank sum test were used to compare proportions and medians, respectively.

Results

Induction therapy

Patient characteristics, including histology, are detailed in Table I for 253 evaluable patients. Forty-eight patients were not evaluable for the reasons shown in Table II. A CR occurred in 145 of the 253 evaluable patients (57%; 95% CI, [51%, 64%]), and an additional 93 patients achieved a PR (37%; 95% CI, [31%, 43%]), for an overall response rate of 94%

Table I. Characteristics of 253 patients eligible for induction stage.

Characteristics	No.	%
Age		
>40 years	74	29.2
≤40 years	179	70.8
Sex		
Males	181	71.5
Females	72	28.5
Race		
Caucasians	231	92.0
Black	15	5.9
Others	5	2.8
PS		
0	90	35.6
1	133	52.6
2–4	30	11.9
Histology		
NS	125	49.4
MC	98	38.7
Others	30	11.9
Stages		
Stage III	127	50.2
Stage IV	124	49.0
Missing data	2	0.8
B symptoms	215	85.0
No B symptoms	38	15.0
Extranodal sites involved		
0	76	30.0
1	91	36.0
≥2	50	19.8
Unknown	36	14.2
Organs involved		
Lung	46	18.2
Liver	74	29.2
Marrow	52	20.6
None of the above	112	44.3

PS, performance status; NS, nodular sclerosis; MC, mixed cellularity.

Table II. Reasons for ineligibility for induction stage.

Entered	301
Eligible	253
Ineligible	48
Reasons for ineligibility	
Cancelled before treatment-unreliable data	2
Refused treatment	1
Ineligible after central review	21
Prior RT to involved site	5
Ineligible stage	3
No measurable disease	5
Not HD	4
Prior chemotherapy	1
Progression before treatment	1
Severe thrombocytopenia of unknown etiology	1
Unclear reason	1
Pathology changed on central review to:	24
Non-Hodgkin lymphoma	21
Malignant histiocytosis	1
Atypical benign hyperplasia	1
Composite lymphoma	1

with a 95% CI of [90%, 97%]. Three patients had stable disease, seven had progressive disease, and five were unevaluable for response. Neither gender, presence or absence of B symptoms, pathological stage, performance status, age >40 years, histological subtype, parenchymal organ involvement, marrow involvement, nor number of extranodal sites involved significantly influenced the attainment of CR. However, age >40 years and performance status of 2 or higher adversely significantly influenced the overall response status (CR/PR) to induction therapy ($p = 0.04$, $p = 0.02$, respectively) (Table III).

Toxicity data were collected and analyzed for a total of 298 patients, including ineligible patients, who received any MOPP-Bleo induction therapy. There were two grade five toxicities; one patient died of pulmonary infection and another of hemorrhage. Grade 4 thrombocytopenia occurred in 5% of patients and grade 4 leukopenia was observed in

6%. Only 5 (2%) grade 4 infections occurred. Grade 3 thrombocytopenia and leukopenia occurred in 7% and 22% of patients, respectively.

Consolidation therapy

A total of 178 responders were registered for the consolidation step with ABVD or RT. The major reasons as to why the 60 responders were not registered include patient's refusal of further treatment, and progression or death before consolidation randomization. Of 178 registered responders, 164 were considered eligible and analyzable for the consolidation step (six patients were cancelled and did not receive the assigned treatment, four patients had treatment violations during induction therapy and four patients were directly assigned to ABVD because of marrow involvement after completion of induction therapy), with 114 induction CRs (55 to

Table III. Baseline patient characteristics and response to induction therapy.

Characteristics	No.	CR (%)	p value*	CR + PR (%)	p value†
Male	181	100 (55.2)	NS	170 (93.9)	NS
Female	72	45 (62.5)		68 (94.4)	
Age					
≤40	179	105 (58.7)	NS	172 (96.1)	
>40	74	40 (54.1)		66 (89.2)	0.0432
Stage III	127	75 (59.1)	NS	121 (95.3)	NS
Stage IV	124	69 (55.6)		115 (92.7)	
Missing data	2	1 (50.0)		2 (100.0)	
No B symptoms	38	23 (60.5)	NS	35 (92.1)	NS
B symptoms	215	122 (56.7)		203 (94.4)	
PS					
0	90	54 (60.0)	NS	88 (97.8)	0.0226
1	133	74 (55.6)		125 (94.0)	
2–4	30	17 (56.7)		25 (83.3)	
NS	125	65 (52.0)	NS	117 (93.6)	NS
MC	98	59 (60.2)		94 (95.9)	
Other histology	30	21 (70.0)		27 (90.0)	
Extranodal sites					
0	76	47 (61.8)	NS	72 (94.7)	NS
1	91	51 (56.0)		84 (92.3)	
≥2	50	30 (60.0)		48 (96.0)	
Missing data	36	17 (47.2)		34 (94.4)	
Lung involved					
No	203	119 (58.6)	NS	192 (94.6)	NS
Yes	46	22 (47.8)		42 (91.3)	
Missing data	4	4 (100.0)		4 (100.0)	
Liver involved					
No	173	105 (60.7)	0.0927	162 (93.6)	NS
Yes	74	36 (48.6)		70 (94.6)	
Missing data	6	4 (66.7)		6 (100.0)	
Marrow involved					
No	200	111 (55.5)	NS	188 (94.0)	NS
Yes	52	33 (63.5)		49 (94.2)	
Missing data	1	1 (100.0)		1 (100.0)	

PS, performance status; NS, nodular sclerosis; MC, mixed cellularity; CR, complete response; PR, partial response.

* p -value is from two-sided test comparing the distribution of the characteristic among patients with or without a complete response.

† p -value is from two-sided test comparing the distribution of the characteristic among patients with CR or PR *versus* non-responders.

ABVD and 59 to RT) and 50 induction partial responders (PRs) (25 to ABVD and 25 to radiation, respectively). There is no significant difference in potentially important prognostic factors between the two consolidation treatment groups. Thirty-four (68%) of the patients with PR were converted to CR with consolidation therapy, 16 with ABVD, and 18 with RT. The conversion rates were not significantly related to treatment or any patient characteristics analyzed. Therefore, of 253 eligible and analyzable patients on the induction step there were 179 (71%) patients whose best response was CR; 145 (81%) of those achieved CR with induction treatment and 34 (19%) with consolidation therapy.

Toxicity was evaluated for a total of 199 patients who received consolidation therapy. Consolidation therapy was, in general, well tolerated. Patients randomized to RT had a higher incidence of grade 4 thrombocytopenia than did those randomized to ABVD (10% vs. 1%, $p=0.004$), while there was a trend toward a higher incidence of grade 3–4 neutropenia in the ABVD group (4% vs. 0%). Grade 3 vomiting was significantly more frequent with ABVD than with RT (18% vs. 3%, $p=0.0005$). There was one toxic death with each treatment option. A patient who received radiation consolidation died of acute myeloid leukemia, and a patient treated with ABVD died of presumed bleomycin pulmonary toxicity. Other adverse events with either therapeutic option were minor, infrequent, or absent.

DFI was significantly longer for induction patients with CR consolidated with ABVD compared with radiation (HR = 0.54; 95% CI, 0.29–1.0; $p=0.05$; Figure 2). At 20 years, DFI was 70% for ABVD vs. 52% for radiation. A potential interaction between pathology type and treatment groups for induction

Figure 2. Kaplan-Meier estimate for disease-free interval by treatment arm among 114 eligible and analyzable patients in consolidation step with a CR at the time of randomization. p -value is from stratified log rank test with age group as strata. To view in colour online please go to: www.informahealthcare.com/lal.

patients with CR was suggested. ABVD significantly prolonged DFI only in 63 patients with pathology other than nodular sclerosis ($p=0.03$). Twenty-five PRs were randomized to each of the consolidation treatments. For 34 patients, who had a PR converted to CR by consolidation therapy, the DFI was considered to have begun at documentation of CR. Sixteen of those patients were randomized to ABVD and half have relapsed, while 18 patients were randomized to RT and 4 (22.2%) have relapsed. There was a trend toward a better outcome with RT compared with ABVD in this small group of patients ($p=0.09$), Intent to treat analyses including all 190 patients randomized to consolidation yield identical results. For all patients with a best response of CR 62% (95% CI, [58%–66%]) remain in CR at 20 years, with no significant difference in CR duration between induction CRs and patients who achieved CR during consolidation ($p=0.77$). Of the 114 patients with a CR at the time of randomization to consolidation therapy, 55 were randomized to ABVD and 18 (33%) of those eventually relapsed. Fifty-nine were randomized to RT and 31 (54%) relapsed (HR = 0.49; 95% CI, 0.28–0.89; $p=0.02$; Figure 3). Of the 50 patients with a PR at the time of randomization to consolidation therapy, 25 were randomized to each arm and 14 (56%) failed after ABVD, compared with 12 (48%) who failed after RT ($p=0.58$). Similarly as in DFI, ABVD significantly prolonged the PFS only in patients with pathology other than nodular sclerosis ($p=0.01$). An intent-to-treat analysis of all 190 patients yields identical results.

With a median follow-up of 21.3 years for the 164 induction therapy responders, 73 (45%) have died,

Figure 3. Kaplan-Meier estimate for progression-free survival by treatment arm for the 114 eligible and analyzable patients in consolidation step with a CR at the time of randomization for consolidation. p -value is from stratified log rank test with age group as strata. To view in colour online please go to: www.informahealthcare.com/lal.

including 26 (33%) of the 80 patients who received ABVD consolidation and 47 (56%) of the 84 patients consolidated with RT. Of all 148 patients with CR, 62 (42%) have died as did 11 (69%) of the 16 patients with PR. The OS rates for all 164 patients at 5, 10, 15, and 20 years were $80\% \pm 3\%$, $66\% \pm 4\%$, $59\% \pm 4\%$, and $54\% \pm 4\%$, respectively. The 20-year estimated OS rate for 80 patients consolidated with ABVD was 66%, compared with 43% for 84 patients consolidated with RT (HR = 0.49; 95% CI, 0.30–0.79; $p = 0.002$; Figure 4). Similarly as with DFI and PFS, further analysis indicates there is no treatment difference for patients classified as nodular sclerosis ($p = 0.33$), while the ABVD group had a significantly longer survival than the radiotherapy group for patients with pathology other than nodular sclerosis (stratified log-rank test, $p = 0.006$). If the data for all 253 patients are analyzed from induction registration, ABVD remains a highly significantly superior consolidation therapy compared with RT ($p < 0.001$, Table VII).

Prognostic factors

Important prognostics factors, including sex, age, performance status, pathologic stage, presence of B symptoms, histology, lung, liver or marrow involvement, and number of extranodal sites, were evaluated in univariate analysis and multivariate Cox proportional hazard models for 114 induction patients with CR in DFI, PFS, and OS analysis. Initially, stage III disease ($p = 0.043$) and no marrow involvement (0.02) predicted a longer DFI (all log-rank two-sided p values, Table IV). When stage effect, marrow involvement, and gender effect were

Figure 4. Kaplan-Meier estimate for survival by consolidation arms among 164 induction responders deemed eligible and analyzable in consolidation step by consolidation treatment. p -value is from stratified log rank test with age group as strata. To view in colour online please go to: www.informahealthcare.com/lal.

adjusted using a stratified proportional hazard regression model, the difference in DFI between the two consolidation treatments was marginal ($p = 0.07$). Two factors were found to influence the distribution of PFS (Table V): age < 40 years old *versus* older patients (20-year PFS: 63% *vs.* 37%; $p = 0.05$), and patients with *versus* those without bone marrow involvement at presentation (20-year PFS: 62% *vs.* 37%; $p = 0.02$). Furthermore, there was a trend toward greater 20-year PFS in females and those with mixed cellularity histology (Table V).

Table IV. Influence of selected factors on survival of evaluable patients.

Variable	No. of patients	No. died	% Survival at 15 years	<i>p</i>
All patients	253	130	52	
Consolidation treatment				
ABVD	87	30	65	
RT	92	51	51	
Others	74	49	38	<0.0001
Sex				
Males	181	97	51	
Females	72	33	55	NS
Age				
≤40	179	75	62	
>40	74	55	29	<0.0001
PS				
0	90	39	57	
1	133	74	50	
2–4	30	17	46	NS
Pathologic stage				
III	127	60	56	
IV	124	68	49	
Missing data	2	2	0	NS
B symptoms				
No	38	21	49	
Yes	215	109	53	NS
Histology				
NS	125	69	50	
MC	98	44	58	
Others	30	17	43	NS
Lung involvement				
No	203	107	51	
Yes	46	21	57	
Missing data	4	2	75	NS
Liver involvement				
No	173	86	53	
Yes	74	42	48	
Missing data	6	2	67	NS
Marrow involvement				
No	200	96	54	
Yes	52	33	46	
Missing data	1	1	0	0.09
Number of extranodal sites involved				
0	76	34	56	
1	91	55	47	
≥2	50	28	48	
Missing data	36	13	64	NS

ABVD, adriamycin, bleomycin vinblastine and dacarbazine; RT, radiation therapy; NS, not significant; PS, performance status; NS, nodular sclerosis; MC, mixed cellularity.

Table V. Influence of various factors on disease free interval of induction therapy complete responders.

Factor	Total patients with CR	No. relapsed	DFS @ 20 years (%)	<i>p</i>
All patients	114	42	61	
Consolidation treatment				
ABVD	55	16	70	0.05
RT	59	26	52	
Sex				
Male	79	33	56	0.08
Female	35	9	72	
Age				
< 40	84	29	65	NS
> 40	30	13	47	
Performance status				
0	40	13	65	NS
1	58	22	61	
2–4	16	7	54	
Pathologic stage				
III	60	17	70.3	0.043
IV	53	24	52.3	
Missing data	1			
B symptoms				
No	17	7	52	NS
Yes	97	35	62	
Histology				
NS	51	22	57	NS
MC	45	11	74	
Others	18	9	41	
Lung involvement				
No	91	33	62	NS
Yes	19	8	57	
Missing data	4			
Liver involvement				
No	81	29	63	NS
Yes	29	12	55	
Missing data	4			
Marrow involvement				
No	89	29	66	0.02
Yes	24	13	41	
Missing data	1			
Number of extranodal sites involved				
0	37	12	66	NS
1	35	17	49	
> 2	26	11	55	
Missing data	16			

CR, complete response; DFS, disease-free survival; RT, radiation therapy; NS, not significant; NS, nodular sclerosis; MC, mixed cellularity; ABVD, adriamycin, bleomycin vinblastine and dacarbazine.

When adjustments were made for age, gender, histology, and initial bone involvement in a multivariate proportional hazard model, the significance of the effect of ABVD in prolonging PFS remains ($p=0.03$).

In OS analysis, those patients <40 years old had a significantly greater OS compared with older patients ($p=0.006$: Table VI; Figure 5), and there was a trend toward greater 20-year survival for patients with mixed cellularity histology compared with those

Table VI. Influence of various factors on progression-free survival of induction therapy complete responders.

Factor	Total patients with CR	No. relapsed	PFS at 20 years (%)	<i>p</i>
All patients	114	49	56	
Consolidation treatment				
ABVD	55	18	66.8	0.021
RT	59	31	45.6	
Sex				
Males	79	38	51.1	0.085
Females	35	11	67.1	
Age				
< 40	84	31	62.5	0.046
> 40	30	18	36.8	
Performance status				
0	40	15	60.4	NS
1	58	26	55.0	
2–4	16	8	49.2	
Pathologic stage				
III	60	22	62.8	0.11
IV	53	26	49.4	
Missing data	1			
B symptoms				
No	17	9	44.9	NS
Yes	97	40	57.9	
Histology				
NS	51	23	54.9	0.077
MC	45	14	67.8	
Others	18	12	30.1	
Lung involvement				
No	91	38	56.9	NS
Yes	19	9	52.6	
Missing data	4			
Liver involvement				
No	81	33	58.6	NS
Yes	29	14	49.5	
Missing data	4			
Marrow involvement				
No	89	34	61.5	0.02
Yes	24	14	36.8	
Missing data	1			
Number of extranodal sites involved				
0	37	14	61.1	NS
1	35	19	45.1	
≥2	26	12	51.3	
Missing data	16			

ABVD, adriamycin, bleomycin vinblastine and dacarbazine; PFS, progression-free survival; RT, radiation therapy; NS, not significant; NS, nodular sclerosis; MC, mixed cellularity.

with other histologies ($p=0.065$). The statistical significance of survival comparisons between consolidation therapies did not change appreciably by adjusting for age and histology using the multivariate proportional hazard model.

Discussion

Among the 253 eligible and analyzable patients who received induction therapy in this study 145 (57%,

Figure 5. Kaplan-Meier estimate for survival by age group among 164 induction responders deemed eligible and analyzable in consolidation step by age group. To view in colour online please go to: www.informahealthcare.com/lal.

95% CI [51%; 64%]) achieved CR after induction therapy and 238 (94%, 95% CI [90%; 97%]) achieved a CR or PR.

DFI and PFS are significantly greater after ABVD consolidation than after involved field radiation for patients who achieved CR from induction therapy, and survival was significantly prolonged by ABVD for all induction responders (CR/PR). The superior outcome with ABVD consolidation may be primarily for patients with pathology other than nodular sclerosis [5,6]. The overall 71% CR rate for patients in this study, 22% of whom had involvement at more than one extranodal site is compatible with the results of Pillai *et al.* [7] in a similar group of patients treated with similar induction therapy, and with those of Sullivan *et al.* [8] obtained in children with involved field RT followed by MOPP-Bleo. It is also similar to the CR rate with MOPP alternating with ABVD as induction therapy reported by Canellos *et al.* [9]. The 57% CR rate obtained from induction therapy in this study is identical to that reported by Diehl *et al.* [10] with COPP-ABVD, and the CR+ PR rate of 94% after induction and consolidation therapy compares favorably with the 86% CR+ PR rate obtained by Fermé *et al.* [11] in similar patients treated with MOPP or MOPP alternating with ABVD followed by 40Gy total or subtotal nodal irradiation. In a subsequent much larger study, Fermé *et al.* [12] induced 559 patients with MOPP alternating with ABV or a similar regimen and then randomized major responders to receive two additional MOPP/ABV cycles (or similar regimen), or subtotal or total nodal RT. In some groups, the 5-year estimate of survival was better ($p=0.002$) after chemotherapy consolidation than after RT consolidation. The authors concluded that consolidation with radiation was not superior to consolidation

with chemotherapy and after 10 years of follow-up the results and the author's conclusions remain the same [13]. Diehl *et al.* [10] found no difference in outcome when 20 Gy involved-field RT was compared with one course of COPP+ABVD as consolidation therapy in patients who achieved CR after six cycles of alternating induction chemotherapy (COPP – ABVD). Subsequently, Weiner *et al.* [14] conducted a study in pediatric patients in which 183 children and adolescents with stages IIB, IIIA₂, IIIB, and IV were randomized to receive eight cycles of MOPP alternating with ABVD with or without low-dose total nodal radiotherapy. Event-free and OS were 79% and 96%, respectively, at 5 years for patients who were treated with chemotherapy alone and was not significantly improved by consolidation with RT. Nachman *et al.* [15] and Hutchinson *et al.* [16] reported findings from large pediatric randomized trials that are in essential agreement with Weiner *et al.*, [14] in that neither study did consolidation RT improve OS.

Several studies in adults have found that RT consolidation of advanced stage complete responders to chemotherapy may improve failure-free [16] or relapse-free [17] survival, but not OS [16,17], compared with no post-remission therapy.

In a large meta-analysis, RT for advanced stage patients in CR after chemotherapy led to a significantly inferior long-term outcome [18]. However, the methodology of this study has been severely criticized by Prosnitz [19].

An important large study addressing the efficacy of adjuvant involved field RT for advanced –stage patients was reported by Aleman *et al.* [20]. Patients with previously untreated stage III or IV Hodgkin lymphoma who were in CR or PR after MOPP-ABV were randomized to receive no further treatment or involved field RT. Of 739 patients entered, 421 (57%) had a CR; 161 were randomized to no further treatment and 172 to involved-field RT. Twenty-one percent of patients were not randomized for various reasons. The median follow-up was 79 months. For CRs to induction therapy, there was no difference in the 5-year event-free survival ($p=0.35$) and only a trend toward better OS in the adjuvant RT group (91% *vs.* 85%, $p=0.07$). However there was some evidence that RT may have benefited patients with PR after chemotherapy, which was stronger with longer follow-up [21]. This study was praised by Prosnitz [20] and yielded results similar to those obtained in the present study from adjuvant RT.

The 67% PFS at 20 years obtained in this study with ABVD consolidation after MOPP-Bleo induction therapy in patients with advanced Hodgkin

lymphoma compares favorably with results of other studies discussed above, and others [22,23] in which RT was given after induction therapy with an anthracycline-containing regimen.

Although the Stanford V regimen has become popular [24,25], no randomized studies, including the present one with its unusually long follow-up, have been reported in which an advantage for consolidation RT in patients with advanced stage disease has been clearly documented [22,26–27].

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