Symposium article

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ABVD versus Stanford V versus MEC in unfavourable Hodgkin's lymphoma: results of a randomised trial

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Background: Between January 1996 and April 2000, 355 patients with advanced Hodgkin's disease (HD) (stage II bulky disease, III and IV) were enrolled in a prospective, multicentre, randomised trial aimed at comparing the efficacy of two new promising regimens: Stanford V and MEC hybrid. ABVD was chosen as the control arm. Radiotherapy was planned at the end of induction therapy on residual masses or on sites of previous bulky lesions. One hundred and seventeen, 123 and 115 patients were treated with Stanford V, MEC and ABVD, respectively. The records of 275 enrolled patients (89 Stanford V, 88 MEC, 98 ABVD) have been reviewed and are the subject of this report.

Results: After induction therapy a complete response (CR) was observed in 93, 89 and 74% of patients treated with MEC, ABVD and Stanford V, respectively, with a statistically significant difference (P = 0.013) between the arms. After a median follow-up of 24 months, 16 relapses have been recorded among 196 patients who achieved a CR. Relapse rates are 16, 6 and 4% for Stanford V, ABVD and MEC, respectively (P = 0.042). The 3-year survival was 93%, without any significant difference among the arms. However, a significant difference emerged in terms of failure free survival (FFS). Patients treated with Stanford V did the worst compared with those treated with ABVD or MEC (P = 0.001). Toxicity was comparable in the three treatment arms.

Conclusion: For this randomised study, both ABVD and MEC gave superior results to Stanford V in terms of response and FFS; MEC seems to be the best regimen in terms of relapse-free survival, even if a significant difference has not yet been achieved. Notwithstanding the short follow-up, these results seem to be very impressive in defining the best standard treatment for HD for this subset of patients.

Key words: ABVD versus Stanford V versus MEC, chemotherapy, clinical trials, Hodgkin's lymphoma

Introduction

Since the demonstration in the early 1990s by Canellos [1] of its superiority over MOPP (mechloretamine, vincristine, procarbazine, prednisone), ABVD (doxurubicin, bleomycin, vinblastine and dacarbazine) still represents the standard therapy for patients with advanced Hodgkin's lymphoma (HL). However, in recent years different regimens have been proposed for patients with advanced HL, including MOPP/EBV/CAD (MEC) [2], Stanford V [3] and BEACOPP (bleomicin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisone) [4]. In particular, very promising 5-year survival rates of 89% and 96% have been reported with MEC [2] and Stanford V [3, 5], respectively. In 1996, the 'Intergruppo Italiano Linfomi' started a prospective, multiinstitutional trial aimed at assessing the efficacy of Stanford V and MEC compared with ABVD. Here we present the preliminary results of this trial, which closed in April 2000, with the final accrual of 355 patients.

Patients and methods

Between January 1996 and April 2000, 355 patients with advanced HL from four Italian cooperative groups (Gruppo Multiregionale per lo Studio dei Linfomi, GISL (Gruppo Italiano Studio Linfomi), Non Hodgkin's Lymphoma Cooperative Study Group and Gruppo Lombardo per lo Studio dei Linfomi) were randomised after stratification for cooperative group. Patients with the following characteristics were eligible for the trial: biopsy-proved HL; age 15–65 years; stage IIB, II or IV disease; no prior treatment for HL. All patients gave informed consent. Patients were randomly assigned to receive six courses of ABVD, 12 weeks of Stanford

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V or six courses of MEC (Table 1). Involved field radiotherapy was allowed at the end of induction therapy on sites of residual masses or on previous bulky disease. At the time of the present analysis, the records of 275 patients have been reviewed at the centralised trial office, and are the subject of this report. Ninety-eight patients were treated with ABVD, 88 with MEC and 89 with Stanford V. All data were analyzed with the Statistical Package for the Social Sciences (SPSS). Differences in patient characteristics and response rates, among the three groups were analyzed by the Fisher's exact test for contingency tables. Survival, relapse-free survival (RFS), and failure-free survival (FFS) curves were estimated by the method of Kaplan–Meier. The log-rank test was used to assess the significance of differences in survival, RFS or FFS, for each prognostic factor. No statistical differences were registered between the characteristics of the three groups of patients (Table 2).

Table 1. Chemotherapeutic regimens employed in the study

Drug	Dose (mg/m^2)	Route	Days/weeks
ABVD			
Adriamycin	25	i.v.	Days 1–15
Bleomycin	5	i.v.	Days 1–15
Vinblastine	6	i.v.	Days 1–15
Dacarbazine	375	i.v.	Days 1–15
MEC			
Meclorethamine	6	i.v.	Day 1 (courses 1, 3 and 5)
CCNU	100	Oral	Day 1 (courses 2, 4 and 6)
Vindesine	3	i.v.	Day 1
Alkeran	6	Oral	Days 1–3
Prednisone	40	Oral	Days 1–14
Epidoxorubicin	40	i.v.	Days 8
Vincristine	1.4	i.v.	Days 8
Procarbazine	100	Oral	Days 8–14
Vinblastine	6	i.v.	Day 1
Bleomycin	10	i.v.	Day 15
Stanford V (one course, 12 weeks)			
Adriamycin	25	i.v.	Weeks 1, 3, 5, 7, 9, 11
Vinblastine	6	i.v.	Weeks 1, 3, 5, 7, 9, 11
Meclorethamine	6	i.v.	Weeks 1, 5, 9
Etoposide	60	i.v.	Weeks 3, 7, 11
Vincristine	1.4	i.v.	Weeks 2, 4, 6, 8, 10, 12
Bleomycin	5	i.v.	Weeks 2, 4, 6, 8, 10, 12
Prednisone	40	Oral	qds for 12 weeks

Table 2. Patients characteristics

	ABVD (98 patients)		MEC (88 patients)		Stanford V (89 patients)		*P*
	n	%	*n*	%	*n*	%	
Male gender	52	53	45	51	54	61	0.399
Stage IV	19	20	23	26	23	26	0.501
B-symptoms	71	74	65	75	61	68	0.602
Age >60 years	10	10	9	10	3	3	0.144
HB <12 g/dl	27	28	25	28	20	22	0.620
ESR ≥30	76	78	65	74	65	73	0.748
Elevated LDH	24	26	25	32	25	30	0.707
Bulky	29	30	19	22	25	29	0.387

HB, haemoglobin; ESR, erithrocyte sedimentation rate; LDH, lactate dehydrogenase.

Radiotherapy

Radiotherapy was not routinely associated with chemotherapy, but was administered to areas corresponding to previous bulky involvement or to masses that were only slowly or partially reduced during chemotherapy. Radiotherapy had to be administered after chemotherapy and total doses could not exceed 35 Gy. The decision to treat, which sites to treat, and what dose to deliver was left up to the clinicians and radiotherapists of each institution. Radiotherapy was delivered to 65% of Stanford V and ABVD group patients and to 44% of MEC group patients. No differences were reported according to treatment in terms of response between patients who received radiotherapy or not.

Results

After registration, eight patients (2.9%) were excluded because they missed the planned response assessment. The remaining 267 patients were evaluated for response, survival, failure free survival (FFS) and relapse-free survival (RFS). The rates of complete responses (CR) were 89.7% for ABVD, 91.5% for MEC and 71.6% for Stanford V. There was a significantly lower CR rate in the group treated with Stanford V ($P = 0.001$).

The overall 3-year survival rates were 94.7, 95.5 and 89.9% for ABVD, MEC and Stanford V, respectively ($P = 0.217$) (Figure 1). The 3-year FFS rate was 81.4% for ABVD, 86.6% for MEC and 53.4% for Stanford V. A significantly lower FFS was observed for patients treated with Stanford V ($P = 0.0001$) (Figure 2). Relapses occurred in 6.9, 4 and 17.5% of patients treated with ABVD, MEC and Stanford V, respectively. The 3-year RFS rate was 91.5% for ABVD, 94.9% for MEC and 75.7% for Stanford V (Figure 3). The differences in terms of RFS were statistically significant ($P = 0.0126$).

Discussion

The preliminary analysis of the first 275 patients enrolled in the Italian Intergroup HD9601 trial demonstrated the superiority of ABVD and MEC over Stanford V in terms of CR rates, 3-year relapse free survival and 3-year failure free survival. Since the radiotherapy was not mandatory, we analysed responses and duration of remission in patients treated or not with radiotherapy and no differences emerged between these two groups. As far as relapses were concerned they were equally distributed in the two groups.

In all of the three groups, the response was evaluated at the end of treatment and was defined clinical or instrumental CR when all involved areas were completely cleared of disease. This could explain the lower CR rate for the Stanford V group. Our results compare with the 75% of CR reported by Horning et al. [5] in their original report.

In the paper by Horning et al. [5], radiotherapy was indicated as mandatory for all patients. In contrast, in our trial radiotherapy was planned only in patients with residual

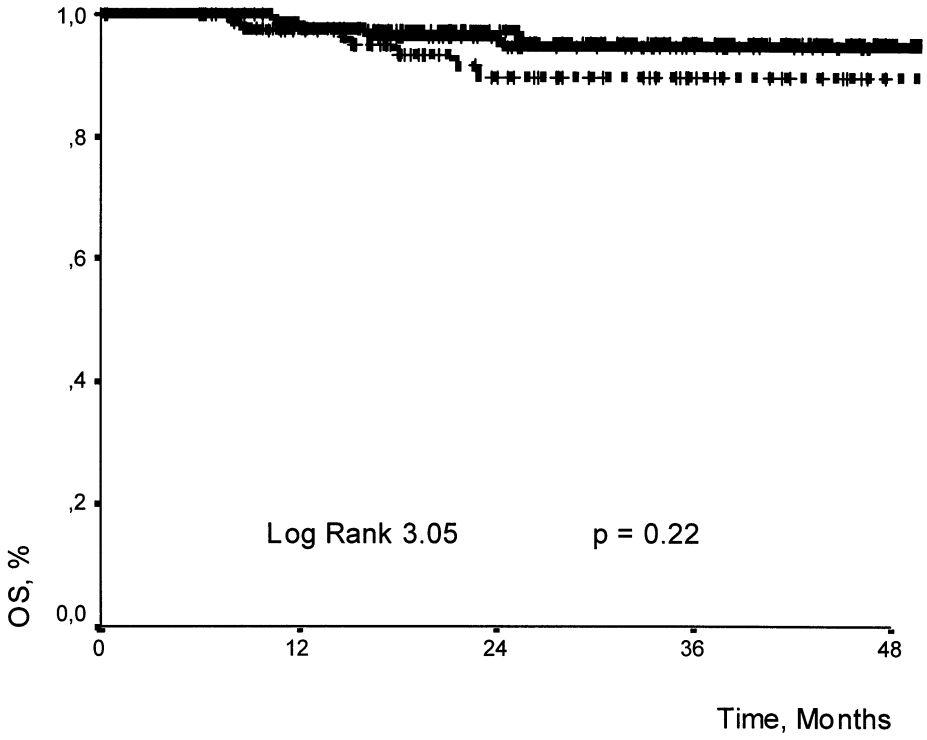

Figure 1. Overall survival of 267 patients, by treatment arm. Projected overall survival after 3 years: ABVD, 94.7%; MEC, 95.5%; Stanford V, 89.9%. ABVD, solid line; MEC, dashed line; Stanford V, pointed line.

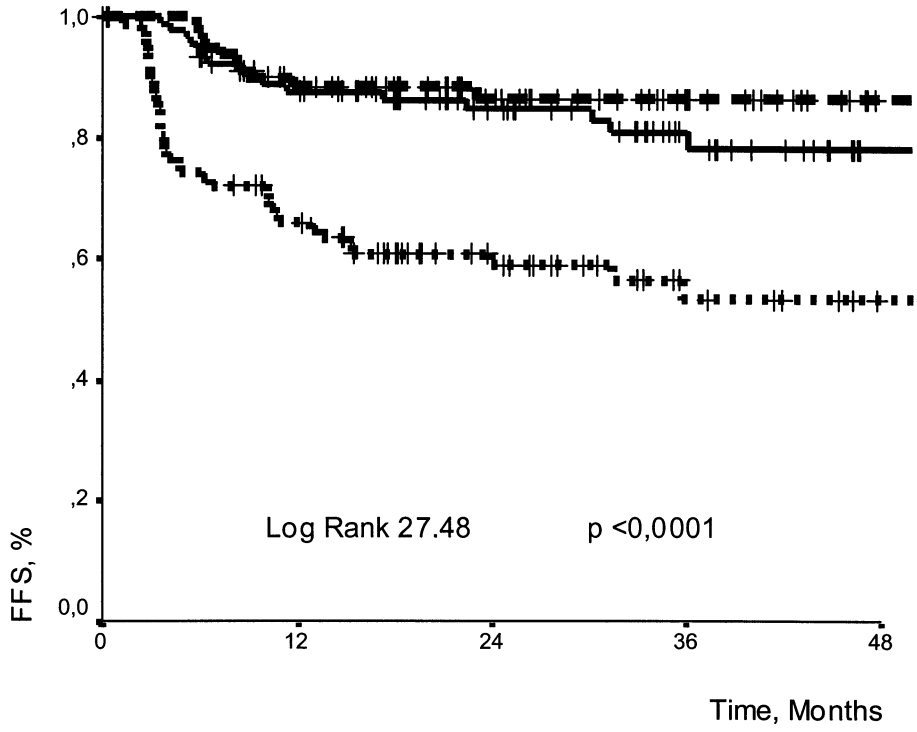

Figure 2. FFS of 267 patients, by treatment arm. Projected FFS after 3 years: ABVD, 81.4%; MEC, 86.6%; Stanford V, 53.4%. ABVD, solid line; MEC, dashed line; Stanford V, pointed line.

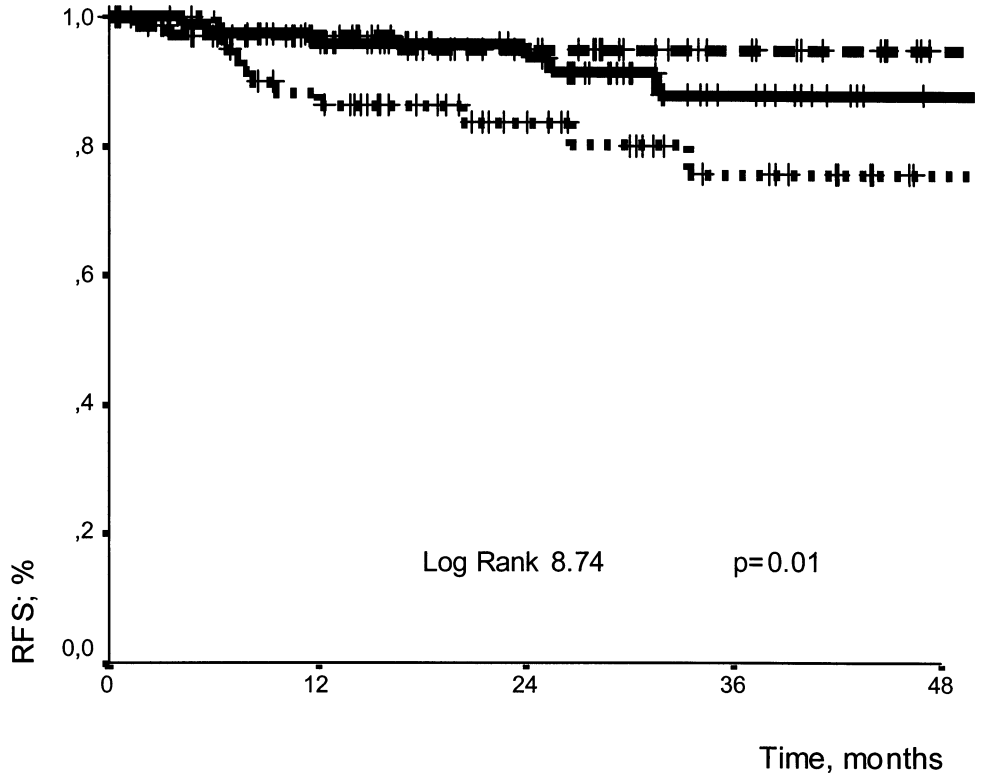

Figure 3. RFS of 225 patients, by treatment arm. Projected RFS after 3 years: ABVD, 91.5%; MEC, 94.9%; Stanford V, 75.7%. ABVD, solid line; MEC, dashed line; Stanford V, pointed line.

masses after chemotherapy or in those with initial bulky disease. As a result, only 65% of patients in the Stanford V arm received radiotherapy. However, the limited use of radiotherapy in our trial apparently did not affect the low response rate associated with Stanford V; in fact the outcome of patients treated or not with radiotherapy was the same in terms of both response and duration of response.

However, the intensified MEC regimen, which was expected to have a major impact on overall response rate (ORR), obtained an ORR comparable to that achieved with ABVD, although a trend toward a better FFS seemed to emerge. A more detailed analysis will be performed when all patients are available for response assessment.

Conclusions

In patients with advanced HL, ABVD and MEC seem superior to Stanford V, as used in the present trial, in terms of ORR, RFS and FFS. At present, no statistically significant differences have emerged in favour of MEC over ABVD.

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