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Chemotherapy versus Radiotherapy in Early-stage Hodgkin's Disease: Evidence of a More Difficult Rescue for Patients Relapsed after Chemotherapy

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Six cycles of mechloretamine, vincristine, procarbazine and prednisone (MOPP) chemotherapy were randomly compared with extended field radiotherapy (RT) in 89 adult patients with pathological stage I–II A Hodgkin's disease (HD). 45 patients received RT and 44 were treated with MOPP. Complete remission (CR) was obtained in all patients in the RT group and in 40 of 44 in the MOPP group. 12 patients relapsed in both groups. 10 out of 44 patients treated with MOPP died of HD, compared with only 2 in the RT group. 3 more patients died in the MOPP group following the occurrence of second cancers. 11 out of the 12 (96%) patients relapsing after RT achieved a second CR, compared with 6 out of the 12 (50%) patients relapsing after MOPP. Analysis of the response rate with salvage treatment, shows that, of the 12 patients who relapsed after MOPP, the pattern of relapse might predict the likelihood of achieving a second CR, whereas in the RT group a second CR was achieved regardless of the characteristics of relapse. Survival probability for relapsing patients at 80 months calculated from relapse was 85% in the RT group and 15% in the MOPP group ($P = 0.02$). With a median follow-up of more than 8 years, the overall survival of patients was significantly better for RT compared with MOPP; 93 and 56%, respectively ($P < 0.001$). On the basis of these results we conclude that, to date, RT alone remains the treatment of choice for adult patients with early-stage HD with favourable prognostic factors.
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INTRODUCTION

THE SUBSTANTIAL data reported to date regarding the treatment of early-stage Hodgkin's disease (ESHD) with chemotherapy (CHT) alone indicate that, despite a high complete remission rate, the long-term survival rate, with a maximum follow-up of 8–10 years, ranges from 39 to 90% [1–3]. These results are similar or in some cases inferior to those reported with the use of extended field radiotherapy. A contentious issue is whether patients relapsing after CHT have a similar probability of successful rescue compared with those relapsing after radiotherapy (RT).

We report the update of a study started on August 1979, in which six cycles of mechloretamine, vincristine, procarbazine and prednisone (MOPP) were randomly compared with extended field RT for the management of pathological stage I–II A Hodgkin's disease.

PATIENTS AND METHODS

From August 1979 to December 1982, 89 consecutive patients with laparotomy-documented stage I–II A HD entered the study. All patients gave informed consent and were treated at the Institutes of Haematology and Radiotherapy of the University "La Sapienza" of Rome and the University of Florence.

Histological classification patterns were according to Lukes and Butler [4]. Pathological stage group II was further divided into stage II[2] and II[3] according to the guidelines of the European Organisation of Cancer Treatment (EORTC) [5].

All patients were randomly allocated to receive one of the following options: (1) RT with "mantle" field followed by para-aortic strip. Radiation dose was 40–44 Gy to involved sites (10 Gy/week in five fractions) and 36 Gy to uninvolved areas, given with a linear accelerator (4–15 MV photons). A 3–4-week rest period was allowed between the "mantle" and para-aortic treatment. (2) Six monthly courses of MOPP according the schedule introduced by De Vita *et al.* [6]. Vincristine dose was capped at 2 mg per total dose.

Response to treatment was evaluated as complete response (CR), defined as the disappearance of any evidence of disease; partial remission (PR), defined as the disappearance of > 50% of any measurable evidence of disease; and non-responders (NR), defined as less than PR.

Relapses were defined according to the following indications: (1) true relapses occurred in previously affected areas (MOPP group) or in areas included in the radiation volume (RT group); (2) lymph nodal extension occurred in previously unaffected areas (MOPP group) or in areas immediately adjacent to the irradiated fields, defined as marginal, or in sites not included in the radiation volume (RT group); (3) dissemination occurred when there was parenchymal involvement regardless of the initial treatment. Patients were followed on a regular basis from August 1979 to February 1991. No patients were lost to the follow-up. The median follow-up was 96 months.

Statistical analysis included Fisher's test (for series up to 50 patients) and χ^2 (for higher series). Disease-free survival (DFS) and overall survival (OS) were evaluated using the Kaplan–Meier method and compared by means of logrank test.

RESULTS

44 patients received MOPP and 45 received RT. As reported elsewhere, the two groups of patients were homogeneous for

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Table 1. Analysis of relapses according to clinical characteristics of patients and treatment modalities

Characteristic	CHT		RT	
	No. of CR patients	Relapses (%)	No. of CR patients	Relapses (%)
All patients	40	12 (30)	45	12 (27)
Sex				
Male	23	10 (43)	19	5 (26)
Female	17	2 (11)	26	7 (26)
Histology				
NS	21	6 (28)	26	7 (27)
MC	16	6 (37)	15	3 (20)
LP	2	0 —	3	1 (33)
LD	1	0 —	1	1 (100)
Stage*				
I–II [2]	18	2 (10)	24	4 (17)
II [3]	22	10 (45)	21	8 (38)
ESR				
≤ 40	27	9 (33)	32	8 (25)
> 40	13	3 (23)	13	4 (31)
Bulky mediastinum				
Yes	8	4 (50)	8	3 (37)
No	32	8 (25)	37	9 (24)

*The pathological stage II was further divided into stage II [2] and II [3] following the guidelines of the European Organisation for Research and Treatment of Cancer (EORTC).
CHT = Chemotherapy; RT = radiotherapy; CR = complete remission; NS = nodular sclerosis; MC = mixed cellularity; LP = lymphocitic prevalence; LD = lymphocitic depletion; ESR = erythrocyte sedimentation rate; *P* values were not significant throughout.

clinical characteristics with respect to age, sex, histology, stage, mediastinal involvement and presence of bulky disease [6] (bulky disease was defined as evidence either of nodes > 5 cm or of a mediastinum–thorax ratio > 0.33).

CR was obtained in all patients in the RT group and in 40 of the 45 patients in the CHT group. 12 patients relapsed in both of the two groups. 30 and 43 patients are alive and free of disease (FOD) in the CHT and RT group, respectively. 10 out of 44 patients treated with MOPP died of their disease, compared to only 2 out of 45 patients treated with RT. 3 more patients in the CHT group died of second cancers (two secondary solid tumours and one secondary acute myeloid leukaemia).

24 out of 89 patients relapsed (12 patients in each group) and, as it is shown in Table 1, the relapse rate, with respect to prognostic factors at diagnosis, was similar in the two groups.

However, the pattern of relapse correlated with the treatment modalities (Table 2). In fact, true relapses were significantly higher in the MOPP than in the RT group (eight out of 12 and one out of 12 relapses, respectively; $P < 0.01$); whereas lymph node extension and/or dissemination of disease was observed in 11 out of 12 patients who relapsed after RT and in 4 out of 12 patients who relapsed after MOPP.

Although not statistically significant, a higher number of early relapses (within 12 months of therapy) was observed in the MOPP group compared with the RT group (Table 2).

All patients relapsing after RT received salvage polychemotherapy consisting of six courses of MOPP in 4 cases and of six courses of alternating MOPP/ABVD in 8 cases. With regard to patients relapsing after MOPP, 4 received a curative extended-field RT, 1 received ABVD alone and the remaining 7 patients

Table 2. Clinical characteristics of relapses in the two groups of treatment

	CHT (12 patients)	RT (12 patients)	*P* value
Type of relapse			
True	8	1	< 0.01
Lymph nodal extension and/or dissemination of disease	4	11	
Time of relapse (months)			
Early (< 12)	9	5	N.S.
Late (> 12)	3	7	

CHT = Chemotherapy; RT = radiotherapy; N.S. = not significant.

received six courses of ABVD combined with extended field RT (6 patients) or six courses of alternating MOPP/ABVD combined with local RT (1 patient).

11 out of the 12 (96%) patients who relapsed after RT achieved a new CR compared with only 6 out of the 12 (50%) patients who relapsed after MOPP. In the RT group a second CR was achieved regardless of type of relapse or in the time of relapse. Conversely of the 12 patients who relapsed after MOPP, the pattern of relapse might predict the likelihood of a second CR. In fact, with respect to type of relapse, only 3 out of 8 patients (30%) with true relapses achieved a second CR, whereas a second CR was observed in 3 out of 4 patients (75%) with lymph node and/or dissemination of disease. Similarly, considering the time of relapse, a second CR was achieved in only 3 out of the 9 patients (33%) with early relapse, whereas all 3 patients relapsed after 12 months from the cessation of MOPP obtained a second CR (Table 3). Figure 1 illustrates the actuarial survival of the relapsed patients according to primary treatment, calculated from time of relapse. The difference between the two groups is statistically significant, resulting at 80 months with 85 and 15% for the RT and CHT group, respectively ($P = 0.02$). In the CHT group, only 2 patients who presented a disseminated and late relapse after MOPP are alive and FOD; whereas among the 12 patients relapsing after RT only 2 of them died of HD.

As expected, the worse outcome of patients relapsed after CHT influenced the overall survival rate of the entire CHT

Table 3. Response to salvage treatment according to the pattern of relapse

Relapse	CHT (12 patients)		RT (12 patients)	
	n	CR (%)	*n*	CR (%)
Type of relapse				
True lymph nodal extension	8	3 (30)	1	1 (100)
+ dissemination	4	3 (75)	11	10 (90)
Time of relapse (months)				
≤ 12	9	3 (33)	5	5 (100)
> 12	3	3 (100)	7	6 (85)

CHT = Chemotherapy; RT = radiotherapy. *n* = Number of patients; CR = number of complete remissions.

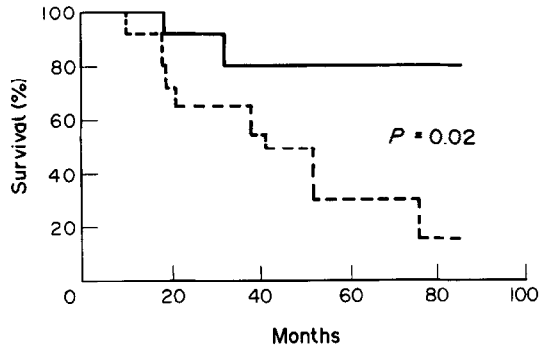

Fig. 1. Actuarial survival of patients relapsing after CHT (----) or RT (——) calculated from time of relapse.

group, which was significantly less than that of the RT group; 56 and 93%, respectively ($P < 0.001$; Fig. 2). Conversely, the 10 years DFS is similar in both groups; 71 and 70% for MOPP and RT, respectively.

DISCUSSION

The results of our study, in which the two modalities of treatment have been compared in two groups of early-stage Hodgkin's disease patients with similar clinical characteristics, show that patients relapsed after MOPP were more resistant to salvage therapy than those relapsing after RT. This may reflect the induction of multi-drug resistant clones after CHT, as suggested by the observation that patients with true and/or early relapses never achieved a durable second CR if initially treated with MOPP. Conversely, the induction of chemoresistance is rarely observed after RT. In fact, this and other clinical studies have demonstrated the effectiveness of CHT programmes as rescue in patients relapsing after RT [7–9]. In some cases the CR rate was even higher in patients who failed previous RT compared with those achieved in patients treated *de novo* [10].

The fact that CHT may induce a higher number of chemo-resistant clones than RT was suggested by several studies in which RT alone was compared to RT+CHT for the treatment of ESHD. Portlock *et al.*, evaluating the impact of salvage treatment on initial relapse in patients with stage I–II HD initially treated either with RT alone or with RT+MOPP, reported that a shorter disease-free interval prior to relapse (suggesting the presence of chemoresistant clones) adversely influenced the effectiveness of subsequent salvage treatment only for patients relapsing after RT+MOPP. Moreover, the median survival of patients relapsing after RT+MOPP was shorter than that of patients relapsing after RT alone [8]. Zittoun *et al.* and Wiernick *et al.* reported a high rate of progressive disease, even after a first successful salvage treatment, for patients with ESHD relapsing after initial treatment with poly-chemotherapy combined with extended or local RT [11, 12]. Finally, Tubiana *et al.*, reporting EORTC lymphoma group data, found in clinical stage I and II HD that the survival rate after relapse was significantly influenced by the initial treatment and that it was lower when it included CHT [13].

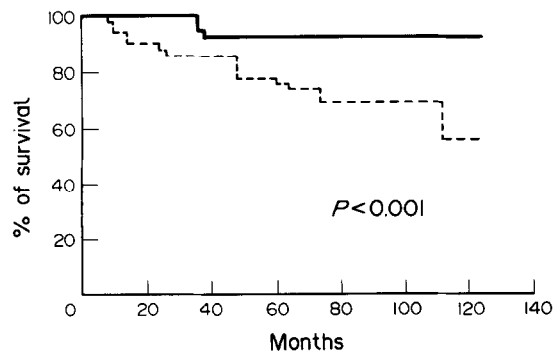

Fig. 2. Actuarial overall survival of patients in the CHT (----) and RT (——) groups.

A direct comparison between MOPP and RT in the treatment of ESHD, is also being carried out by Longo *et al.* in the United States at the National Cancer Institute [14]. With a median follow-up of 7 years, the preliminary results significantly favour MOPP with regard to both DFS and OS, resulting in an apparent contrast with our data. However, it is necessary to underline that these two studies were based on different criteria for the selection of patients. The NCI study included patients with B symptoms, bulky mediastinal masses and stage III A1 disease (all with a worse outcome from radiation alone), whereas patients with peripheral stage I A were not randomised [14]. The criteria used by Longo *et al.* complicate a clear evaluation of the two different therapeutical modalities in ESHD and explain the adverse results sustained with RT.

In conclusion, in our experience to date, RT alone remains the treatment of choice for adult ESHD with favourable prognostic factors. Compared with MOPP, RT achieves a significantly longer survival with less toxicity.

1. Colonna P, Andrieu JM. MOPP chemotherapy alone: a suitable treatment for early stage of HD? *Lancet* 1985, **1**, 1224.
2. Hoppe RT. Early-stage Hodgkin's disease: a choice of treatment or a treatment of choice. *J Clin Oncol* 1991, **9**, 897–901.
3. Cimino G. Chemotherapy alone for the treatment of early stage Hodgkin's disease. *Eur J Cancer* 1990, **26**, 1115–1118.
4. Lukes RJ, Butler JJ. The pathology and nomenclature of Hodgkin's disease. *Cancer Res* 1966, **26**, 1063–1083.
5. Tubiana M, Henry-Amar M, Hayat M, *et al.* Prognostic significance of the number of involved areas in the early stage of Hodgkin's disease. *Cancer* 1984, **54**, 885–894.
6. Cimino G, Biti GP, Anselmo AP, *et al.* MOPP chemotherapy versus extended field radiotherapy in the management of pathological stage I–II A Hodgkin's disease. *J Clin Oncol* 1989, **7**, 732–737.
7. Zagars G, Rubin P. Hodgkin's disease stage I–II A. A long term follow-up study on the gains achieved by modern therapy. *Cancer* 1985, **56**, 1905–1912.
8. Portlock CS, Rosenberg SA, Glatstein E, Kaplan HS. Impact of salvage treatment on initial relapses in patients with Hodgkin's disease, stages I–III. *Blood* 1978, **51**, 825–833.
9. Roach III M, Brophy N, Cox R, Varghese A, Hoppe RT. Prognostic factors for patients relapsing after radiotherapy for early stage Hodgkin's disease. *J Clin Oncol* 1985, **3**, 207–204.
10. Longo DL, Young RC, Wesley M, *et al.* Twenty years of MOPP chemotherapy for Hodgkin's disease. *J Clin Oncol* 1986, **4**, 1295–1306.
11. Zittoun R, Andebert A, Hoerny B, *et al.* Extended versus involved fields irradiation combined with MOPP chemotherapy in early clinical stages of Hodgkin's disease. 1985, **3**, 207–214.
12. Wiernik PH, Gustafson J, Schimpff SC, *et al.* Combined modality of treatment of Hodgkin's disease confined to lymphonodes. Results eight-years later. *Am J Med* 1979, **67**, 183–193.
13. Tubiana M, Henry-Amar M, Carde P, *et al.* Toward comprehensive management tailored to prognostic factors of patients with clinical stage I and II in Hodgkin's disease. The EORTC lymphoma group controlled clinical trials: 1964–1987. *Blood* 1989, **73**, 47–56.
14. Longo DL, Glatstein E, Duffey FL, *et al.* Radiation therapy versus combination chemotherapy in the treatment of early-stage Hodgkin's disease: seven-year results of a prospective randomized trial. *J Clin Oncol* 1991, **9**, 906–917.