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EBVD AND ALTERNATING MOPP/EBVD WITH OR WITHOUT LOCALIZED FIELD RADIOTHERAPY IN ADVANCED OR UNFAVORABLY PRESENTING HODGKIN'S DISEASE

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ABSTRACT

Patients and Methods. **Ninety-five patients with previously untreated, advanced or unfavorably presenting Hodgkin's disease were recruited in ten centers. Twenty-five patients with stage II-A-bulky disease received four courses of EBVD (epirubicin, bleomycin, vinblastine, dacarbazine) plus involved field radiotherapy (Group 1); 24 patients in stage I-B, II-B and III-A received 6 courses of EBVD (11 of them also received radiotherapy on *bulky* localizations (Group 2); 46 patients in stage III-AS ≥ 3 nodes, III-B and IV received MOPP/EBVD 4+4 courses (Group 3).**

Results. **Eighty patients (84%) achieved CR, eight patients (8%) a PR, five patients did not respond and two progressed during therapy. CRs were achieved by 23/25 patients (92%) in Group 1, 21/24 (87%) in Group 2 and 36/46 (78%) in Group 3. The mean duration of follow-up was 33.3 months (range 5-69). There were three deaths from directly treatment-related causes. Twelve patients suffered chronic toxicity, including six who suffered lung toxicity and two who developed secondary myelodysplasia.**

Conclusions. **The results achieved in this co-operative study are similar to those reported by most single-Institution trials and those with adriamycin-containing regimens. Long-term toxicity deserves careful consideration.**

Key words: combined modality therapy, combined modality therapy-toxicity, epirubicin, MOPP/EBVD chemotherapy, Hodgkin's disease-therapy

The years between 1970 and 1980 were characterized by the following steps in the treatment of Hodgkin disease (HD). The introduction of the MOPP combination allowed an 80% complete remission (CR) rate to be achieved,[1] and a cross-over study showed that ABVD was slightly more efficacious than the MOPP regimen and was undoubtedly effective in MOPP-resistant patients.[2] In the years between 1980 and 1990, the superiority of the MOPP/ABVD combination over MOPP alone in patients with stage IV disease was demonstrated;[3] these results have even been challenged recently by the NCI.[4] Between 1975 and 1990 a large number of studies were published that aimed at evaluating prognostic factors and reducing the need for invasive staging procedures. As a consequence, chemotherapy has been used in groups of patients previously treated with radiotherapy alone, and patients with negative prognostic factors have been treated with higher dose intensities.[5-7]

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Since April 1988, the Lombard Co-operative Group for the study and treatment of lymphomas has developed a protocol for the treatment of HD; it has been designed, bearing in mind known results and still unanswered questions, so as to be easily used in a co-operative group with different degrees of specialization. The most distinctive aspects of this protocol are as follows:

1. limited use of staging laparotomy, which has been largely replaced by laparoscopy;
2. treatment of stages I-B and II-B with chemotherapy alone; intensified chemotherapy (6 courses) combined with involved field radiotherapy in bulky stages I-B II-B and III-A;
3. wider use of ABVD-like combinations, because of their known efficacy in the primary therapy of HD[1,2] and the fact that the risks of leukemogenic and cancerogenic effects are lower than with the MOPP combination;
4. replacement of adriamycin by the less cardiotoxic epirubicin; the epirubicin dose is 60% higher than the adriamycin dose in the original protocol;
5. alternating MOPP and EBVD treatment in advanced stages (III-AS ≥ 3 nodes, III-B, IVA and IVB); this therapy is now generally considered superior to MOPP alone, although some controversies still remain.

This paper reports preliminary data (as of March 1994) relating to 95 patients.

Patients and Methods

Patient population

The data reported here refer to 95 patients with previously untreated, advanced or unfavorably presenting HD who were recruited between April 1988 and July 1993 in 10 Centers. Inclusion criteria were: 1) unequivocal histologic diagnosis of HD; 2) age between 14 and 70 years; 3) no previous treatment; 4) advanced or unfavorably presenting disease, defined as stage I-B to IVB, or II-A bulky to IVA; 5) no concurrent cardiocirculatory insufficiency or chronic renal failure.

Patients were investigated according to the staging standards defined by the Ann Arbor Conference and subsequently modified by the Cotswolds Meeting.[8,9] In particular, the staging procedures routinely included chest X-ray (two projections) and thoracic computed tomography (CAT scan) if the chest X-ray was negative or if there was supradiaphragmatic disease; abdominal-pelvic CAT scan, with or without lymphangiography (lymphangiography was performed in all cases of negative or doubtful CAT results); laparoscopy with multiple hepato-splenic biopsies. None of the patients was staged using exploratory laparotomy or splenectomy. Every clinical, radiological or laboratory investigation that disclosed abnormalities at pre-treatment staging was repeated at the end of treatment to evaluate response.

Therapy administration and assessment of response

Depending on the stage of the disease and the presence of *bulky* localizations, patients were treated with three different regimens (see Table 1): 25 patients with stage II-A-bulky received 4 courses of EBVD plus involved field radiotherapy (IFRT) at doses ranging from 30 to 40 Gy (average 35.5) (Group 1); 24 patients with stage I-B, II-B and III-A received 6 courses of EBVD, (11 patients with *bulky* also received local radiotherapy) (Group 2); 46 patients with stage III-AS with ≥ 3 nodes, III-B and IV received MOPP/EBVD 4+4 courses; prednisone (40 mg/sqm/day for 14 days) was also administered

Table 1. Outcome according to treatment group.

	*1**	*2**	*3**	*Total*
CR	23 (92%)	21 (87%)	36 (78%)	80 (84%)
PR	0	2 (8%)	6 (14%)	8 (8%)
NR	2 (8%)	1 (5%)	2 (4%)	5 (5%)
PD	0	0	2 (4%)	2 (3%)
Total	25	24	46	

*CR: complete remission; PR: partial remission; NR: no response; PD: progressive disease. *treatment group: see text for definition.*

during each MOPP course, and the maximum dose of vincristine was limited to 2 mg. (Group 3). EBVD was administered with the following schedule: epirubicin 40 mg/sqm, bleomycin 10 mg/sqm, vinblastine 6 mg/sqm, dacarbazine 375 mg/sqm, days 1 and 15, to be repeated at day 28. Restaging was performed after 4 EBVD or 6 courses of the MOPP/EBVD combination. Cycles were delayed only in the case of severe myelosuppression. Antiemetic therapy was administered with metoclopramide; only a few patients in the last year of the trial received ondansetron.

Remission criteria were defined as follows: complete remission (CR) as a regression of measured lesions and the disappearance of any other objective evidence of lymphoma for at least four weeks; partial remission (PR) as a reduction of 50% or more in the sum of the products of the largest diameters of all measurable lesions, maintained for a period of four weeks; no response (NR) as a less than 50% decrease in the size of measurable lesions; progressive disease (PD) as an increase of more than 25% in the measurable lesions.

Statistical analysis

The overall survival (OS) of eligible patients was calculated from the first day of treatment until death or until the date of the last follow-up examination; all deaths were considered as events. Event free survival (EFS) was measured from the first day of treatment until death, progression, relapse, withdrawal from the protocol or the date of the last follow-up examination; all deaths, relapses, progressions or protocol withdrawals were considered as events. Disease free survival (DFS) was calculated from the date of CR until the first sign of relapse or until the date of the last available follow-up examination; only deaths or withdrawals were considered as events. The log-rank test was used to compare survival in the different groups of patients. Cox's analysis was used to assess the influence of treatment group, average dose intensity and other characteristics at disease onset (ESR, histologic subtype, albumin and LDH serum levels) on OS, DFS and EFS. Dose intensity (DI) analyses were performed using the method of Hryniuk and Bush.[10] Calculation of DI considered the quantity of each drug (mg/sqm) given to treated patients during the first 112 or 168 days when EBVD was used (the days necessary for administering 4 or 6 cycles of EBVD), or 224 days when 8 cycles of MOPP/EBVD were administered. DI is expressed as a fraction of the dose theoretically delivered by the standard protocol over the same period of time.

Table 2. Patient characteristics at onset.

	patients	*%*
Histology		
LP	5	5
NS	25	26
NS-MC	25	26
NS-LD	3	3
MC	26	27
LD	7	7
Unclassifiable	4	4
Stage		
IB	1	1
IIA bulky	25	26
IIB	12	13
IIIA*	12	13
IIIB	19	20
IVA	8	8
IVB	18	19
Age		
mean	35.8	
range	14-69	
Sex		
males	60	63
females	35	37
Primary involved sites		
Nodal	83	87
Extranodal	12	13
Systemic symptoms	50	53
Bulky disease	35	37
Bone marrow involvement	15	16
LDH >500 U	21	22
ESR >30	66	69
Serum albumine < 3 g/dL	7	7
Performance status (ECOG)		
0	47	49
1	41	43
2	6	6
3	1	2

*Legend: LP: lymphocytic prevalence; NS: nodular sclerosis; MC: mixed cellularity. LD: lymphocyte depletion; ESR: erythrocyte sedimentation rate; LDH: lactic dehydrogenase. *one patient with stage III-AS > 3 nodes.*

Results

Of the 112 patients enrolled, 95 were considered assessable for treatment response and toxicity. Seventeen were considered ineligible (13 due to major protocol violation, 1 lost to follow-up and 3 patients who are still receiving induction therapy). Patient characteristics are listed in Table 2. Table 1 shows treatment outcome according to treatment group: overall, 80 patients (84%) achieved CR and 8 patients (8%) achieved a PR; NR was recorded in 5 patients (5) and 2 patients (2%) experienced PD. When outcome is analyzed according to the three treatment groups, CRs were achieved by 23/25 (92%) patients in Group 1, 21/24 (87%) in Group 2 and 36/46 (78%) in Group 3.

As of March 1994, the mean duration of follow-up was 33.3 months (range 5-69). Figures 1, 2 and 3 show OS, EFS and DFS in the three groups. OS for the patients as a whole (Figure 1) was 89%, 83% and 75% at 24, 36 and 48 months, respectively, (95 observations and 15 events). EFS for the patients as a whole (Figure 2) was 78%, 74% and 74% at 24, 36 and 48 months (95 observations and 20 events); DFS for all of the patients in CR (Figure 3) was 84%, 81% and 81% at 24, 36 and 48 months (80 observations and 12 events). Twelve patients (12.6%) relapsed after a mean period of 9.75 months (range 4-28): 2/12 patients were in stage II-A bulky, 3/12 in stage II-B, 1/12 in stage III-A, 3/12 in stage III-B and 3/12 in stage IV. In the two patients with stage II-A bulky, the relapse occurred in the same region as the initial disease (both were submitted to optimal dose of radiotherapy - 40 Gy).

Seven patients underwent ABMT, 4 for progression and 3 for relapse; one of them relapsed

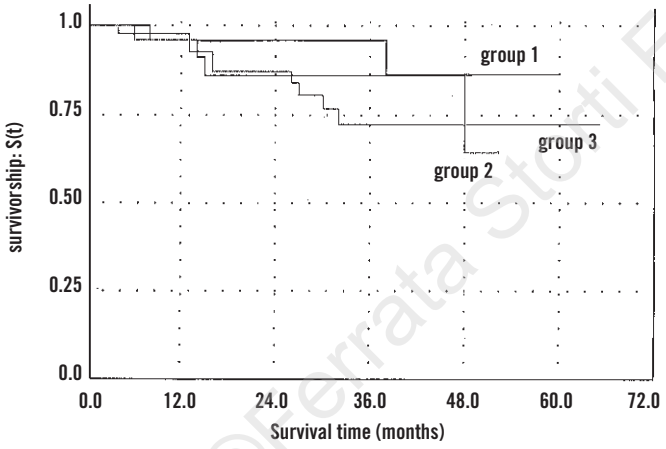

Figure 1. Overall survival in the three treatment groups.

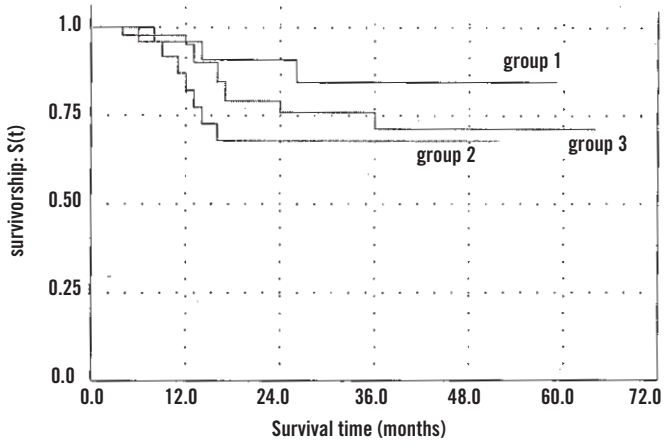

Figure 2. Event-free survival in the three treatment groups.

and died of acute renal failure, one experienced progressive disease and 5 are in CR.

There was no statistical difference in the OS, EFS or DFS of the three groups (Figures 1-3). No prognostic significance for survival could be shown for histologic subtype, ESR, albumin serum levels or LDH serum levels.

Treatment toxicity is summarized in Table 3. WHO grade 3 hematological toxicity was observed in 22/95 patients (23.1%) and WHO grade 4 in 8/95 (8.4%). None of the patients suffered any lethal infectious complications. As far as WHO grade 3-4 extrahematological toxicity is concerned, 59% of the patients experienced nausea/vomiting, 62% alopecia, 5% peripheral neurotoxicity and 6% infections.

Three patients (3.1%) died of causes directly related to therapy: one of myocardial infarction (after 8 courses of chemotherapy), one in stage III-A-bulky of post-radiation pericarditis and sepsis during radiotherapy, and one in stage II-A bulky of post radiation interstitial pneumonia 8 months after radiotherapy was interrupted.

Twelve patients (12.6%) suffered late toxicity (Table 4): pericarditis (2 patients), interstitial pneumonia (2 patients), lung abscess (1 patient), lung fibrosis (4 patients), impotence (1 patient) and myelodysplasia (2 patients).

A total of 15 patients died: 7 from disease progression, 3 from toxicity during first-line therapy and 5 from toxicity during subsequent therapies (1 of acute renal failure, 1 of aplasia, 1 of intracranial hemorrhage and 2 of sepsis).

Dose intensity was calculated for epirubicin and mechlorethamine. The average relative epirubicin dose intensity in the three groups, calculated according to the method of Hryniuk and Bush,[10] was 0.933, 0.931 and 0.809; that of mechlorethamine was 0.862 in the patients treated with EBVD/MOPP. No prognostic significance for DI on survival or on achievement of complete remission could be shown.

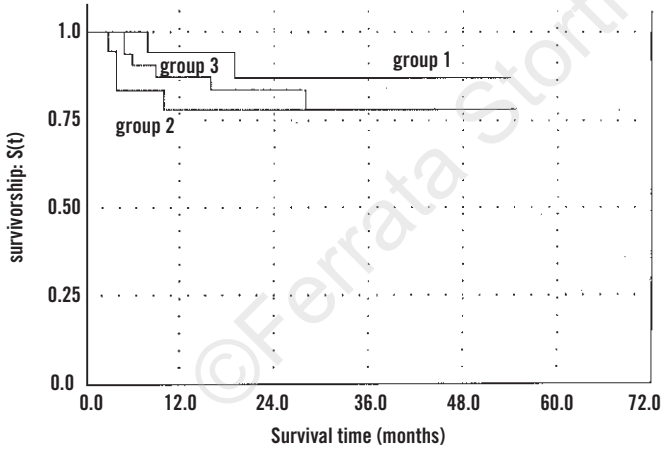

Figure 3. Disease-free survival in the three treatment groups.

WHO grade	*0*	*1*	*2*	*3*	*4*	*evaluable*
Hemoglobin	74 (78%)	5(5%)	13(14%)	3(3%)	0	95/95
WBC	23(24%)	26(27%)	23(24%)	17(18%)	6(7%)	95/95
Platelets	81(85%)	2(2%)	8(9%)	2(2%)	2(2%)	95/95
N/V	5(6%)	8(9%)	23(26%)	33(37%)	19(22%)	88/95
Alopecia	1(1%)	6(7%)	26(28%)	58(60%)	4(4%)	95/95
PNS	49(56%)	30(35%)	4(4%)	4(4%)	1(1%)	88/95
Infections	63(70%)	10(11%)	9(10%)	5(7%)	1(1%)	88/95
Cardiac	84(95%)	2(3%)	1(1%)	0	1(1%)	88/95

N/V: nausea and vomting; PNS: peripheral nervous system.

Table 3. Toxicity.

Table 4. Late toxicity.

Disease	*# of patients*	*Treatment*
Impotence	1	8 MOPP/EBVD
Myelodysplasia	2	8 MOPP/EBVD
		6 EBVD
Pericarditis	2	6 EBVD+RT
		4 EBVD
Lung abscess	1	8 MOPP/EBVD
Interstitial pneumonia	2	6 EBVD+RT
		6 EBVD
Lung fibrosis	4	4 EBVD+RT
		4 EBVD+RT
		4 EBVD+RT
		4 EBVD+RT

Conclusions

In the treatment protocol adopted by the Lombard Co-operative Group staging laparotomy is not used in advanced stages; as a consequence, chemotherapy (using epirubicin-containing regimens) was adopted more extensively than in the period 1975-85.

The results of this co-operative study are similar to those reported by most single-Institution trials and those using adriamycin-containing regimens;[11-24] the CR rate was 92% for stage II-A-bulky, 87% for stages I-B, II-B and III-A, with or without bulky disease; 78% for stages IIIAS (≥3 nodes), III-B and IV (Table 5). These results take on more important significance when the median age (higher than that reported in most groups), the high incidence of B symptoms (52%), bone marrow infiltration (16%) and bulky disease (37%) are considered.

Caution is needed when data regarding OS, EFS and DFS are evaluated because a longer follow-up could reveal a less favorable outcome; however, they must be seen as encouraging because the actuarial estimates of OS, EFS and DFS are all comparable with what has been reported in the literature.[15-19] No significant difference in survival between the three groups was found, possibly (at least in part) due to the short follow-up; in fact, the survival curve of the patients in Group 3 shows reduced values for times longer than 24 and 36 months.

Relative average dose intensity was not found to have any prognostic significance, which may be due to the relatively small number of patients, the short follow-up and/or to the design of the study (which was not primarily created to evaluate dose intensity).

Nevertheless, the fact that 12/95 (12.6%) patients relapsed during a median follow-up of 33.3 months, and bearing in mind the late relapses in Hodgkin's disease, suggests that the ability of the MOPP/EBVD alternating combination to improve the cure rate in cases of advanced stage HD should be evaluated prudently, particularly in the case of patients in stage IV (46% of relapsed patients).

The level of treatment toxicity was acceptable; three of our 95 patients (3.1%) died from causes that were directly related to their treatment (1 case of myocardial infarction, 1 of post-radiation pericarditis+sepsis and 1 of post-radiation interstitial pneumonia), a figure which is in line with other data relating to aggressive regimens already published in the literature. Late toxicity will need to be carefully observed since 12 patients suffered from chronic toxicity over a relatively short follow-up (Tables 7 and 8). We have observed no secondary solid tumors, although two patients have developed myelodysplasia (1 after 8 cycles of MOPP/EBVD and 1 after 6 cycles of EBVD.

A significant number of patients suffered lung toxicity (4 fibroses and 2 interstitial pneumonias), five after combined EBVD and RT and one after EBVD alone. Both radiotherapy and bleomycin alone can cause lung toxicity and their association is known to increase this risk.[22] The toxic effects of bleomycin on lung function in adults is related to the total dose and the patient's age: total doses of less than 500 U were associated with 10% of the cases of clinically evident alterations and with a 1-2% adult mortality rate.[25-28] Since the maximum total dose of bleomycin in our study was never higher than 180 U (and so far from 500 U), the association with RT may have been responsible for toxicity in 5 of these 6 patients. The short follow-up does not allow any conclusions about alterations in fertility; there were 20 patients aged less than 45 in Group 1 (6 males and 14 females), 24 in

Group 2 (9 males and 15 females) and 32 in Group 3 (24 males and 8 females).

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