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Chemotherapy Alone for the Treatment of Early-stage Hodgkin's Disease

INTRODUCTION

THE INTRODUCTION of modern radiotherapy with megavoltage equipment has greatly improved the prognosis of early-stage Hodgkin's disease (ESHD). In 1966 the eradication capacity of radiotherapy was first demonstrated by Kaplan who showed that the risk of recurrence was a function of dose: the proportion of in-field recurrences dropped from 60%–80% with 10 Gy or less to 1.3% at 40 Gy [1]. Thus the possibility of cure of ESHD became a reality, with a change from palliative to radical treatment policy with high-dose radiation and extended-field techniques. Successive improvements of technical and staging procedures, including the use of parallel opposed anterior-posterior portals, linear accelerators, lymphography and surgical laparotomy, resulted in complete response (CR) rates of more than 90% and a high cure rate of more than 85% [2–7]. Nevertheless, differences in technical procedures and radiation delivery equipment can affect the final results, particularly disease-free survival (DFS). Thus results from the many studies of extended-field radiotherapy in ESHD show considerable variation in DFS ranging from 65% to 82.5% at 10 years [2–10]. In addition, infield recurrence rate may vary in relation to the experience of the radiotherapist [11]. Despite this wide variation of DFS, the same studies have shown similar high overall survival (OS), with more than 85% of ESHD patients alive 10 years after initial treatment [2–9]. The differences between DFS and OS are essentially due to the effectiveness of modern chemotherapy in the salvage of patients who relapse after radiotherapy. In the late 1960s, De Vita *et al.* introduced the MOPP regimen (mustine, vincristine, procarbazine and prednisone) into the management of advanced stage Hodgkin's disease [12]. The superiority of MOPP or its derivatives in improving the long-term outlook for relapsing ESHD patients compared with palliative radiotherapy or single-agent chemotherapy was clearly demonstrated by Zagars and Rubin in an historical comparison between two similar ESHD series initially treated with radiotherapy alone, before and after 1969 [13]. On the basis of these observations, chemotherapy was combined with radiotherapy for the treatment of ESHD, especially to improve DFS. Several randomised studies in which combined chemo-radiotherapy was compared with radiotherapy alone demonstrated that DFS could be improved, but again OS was similar with both options [2,14–16]. Moreover, in these studies, an increased frequency of side-effects, including secondary leukaemia, was usually observed.

Nevertheless, chemotherapy compared with radiotherapy has several advantages: (1) it is less expensive and available worldwide; (2) its use is associated with less variable results between institutions; (3) it does not induce abnormal muscle and bone growth; and (4) it does not require accurate staging procedures. Based on these considerations, isolated studies in paediatric patients were started to determine whether chemotherapy alone would be a useful option in ESHD. These studies, although in

small series, showed that MOPP or equivalent combinations achieved CR in almost all cases and induced OS rates from 72% to 100% at 10 years after diagnosis [17–19].

CHEMOTHERAPY VERSUS RADIOTHERAPY

To compare the effectiveness of chemotherapy with that of radiotherapy in the treatment of ESHD, two randomised studies have been done. In 1979 our group initiated a collaborative project in haematological and radiotherapy institutions of the Universities of Rome and Florence, in which six cycles of MOPP were randomly compared with radiotherapy ("mantle" plus "lumbar bar") in 89 adult patients with Hodgkin's disease pathologically staged as I–IIA [20]. Although a higher CR rate was observed in the radiotherapy group, no statistically significant differences were observed between the two treatments for CR, DFS, or OS rates. In addition, no statistical differences were observed in the patients with unfavourable clinical characteristics, such as multiple sites of involvement, bulky mediastinal disease or bulky disease at other sites. In the pattern of relapse, two main differences were observed: firstly, true recurrences [defined as relapses in previously affected areas (MOPP group) or in areas included in the radiotherapy field (radiotherapy group)] were significantly more frequent in patients who received chemotherapy than in those treated with radiotherapy, who relapsed mainly in previously uninvolved sites. Secondly, early relapses (i.e. within 1 year from the end of the treatment) were also more frequent in the chemotherapy group. 10 out of 11 patients relapsed after MOPP compared with 5 out of 11 after radiotherapy. These data suggests that curative radiotherapy achieves better local control of Hodgkin's disease than does chemotherapy. Moreover, since true and early relapses are possible indicators of a less favourable response to salvage treatments, they may indicate a worse prognosis for patients relapsing after MOPP. In this respect, although the difference was not statistically significant, patients relapsing after MOPP had a worse OS rate (45% vs. 76%). This observation accords with the less favourable response to salvage treatment observed by Zittoun *et al.* in patients initially treated with chemo-radiotherapy compared with those treated with radiotherapy alone [16].

The second trial is in progress in the USA at the National Cancer Institute. MOPP alone is being compared with extended-field radiotherapy in pathological stage I (central), IIA and IIB Hodgkin's disease. Results to date show a high CR rate regardless of the initial type of treatment, with duration of CR significantly in favour of MOPP but no difference between the two arms in OS. The study suggests that MOPP may be more effective than radiotherapy in ESHD in terms of DFS [21,22]. However, the inclusion of stage IIB patients may explain the lower DFS rate in the radiotherapy arm, which was not observed in our study [20].

CHEMOTHERAPY ALONE

Few reports are available on the use of chemotherapy alone, and its role in the management of ESHD still has to be elucidated. A summary of the data, showing the main clinical characteristics and response to treatment of 256 ESHD patients (including the 44 of our randomised study) treated with chemotherapy alone, is shown in Table 1. MOPP or MOPP-related regimens achieve an overall CR rate of 88%, while the DFS and OS rates ranged from 62% to 100% and from 72% to 93%, respectively, at 10 years after treatment. 44 of the 226 CR patients (19%) relapsed.

Two aspects deserve emphasis. Firstly, it appears that CHT alone induces a better outcome in younger patients. In the first three series (Table 1), which included only paediatric patients, all 32 cases achieved CR. When compared with the 194 CRs in the remaining 224 patients (87%), there was a significant difference ($\chi^2 = 4.84$, $P<0.05$). Only 3 of the 32 paediatric patients relapsed and the OS rate ranged from 72% to 90% with a follow-up to 8–10 years. These results are in line with those achieved by the combined approaches more widely used for the treatment of childhood Hodgkin's disease, in which a low dose involved-field radiotherapy added to chemotherapy. More recently, the Italian Cooperative Group for Hodgkin's disease reported CR, DFS and OS rates of 100%, 95.4% and 95.5%, respectively in 65 children with ESHD clinically staged I–IIA and treated with three cycles of doxorubicin, bleomycin, vinblastine and decarbazine (ABUD) combined with low doses of involved-field radiotherapy (unpublished). These results were in agreement with the general experience reported in larger series of paediatric patients treated with similar combined strategies [27,28].

Secondly, analysis of the substantial number of patients reported to date confirms our previous observation of the high frequency of true and early relapses among patients with ESHD treated with chemotherapy alone. Data on type and time of relapse were available in 31 and 19 respectively, out of the 44 relapsed patients (Table 1). True recurrences occurred in 26 of the 31 (84%) whereas early relapses occurred in 14 of the 19 (74%). These frequencies are higher than those reported after radiotherapy alone [29] and, again, suggests that better local control of Hodgkin's disease is achieved with radiotherapy.

PROGNOSTIC FACTORS

Several recent studies have focused on the importance of prognostic factors in ESHD. It has become clear that radiotherapy alone might not be sufficient for certain subgroups of patients, while chemo-radiotherapy might result in overtreatment for others. Older age, systemic symptoms, bulky mediastinal disease, raised erythrocyte sedimentation rate and the number of involved lymph-nodal sites are unfavourable prognostic factors that alone or combined may influence DFS or OS in ESHD patients [8,10,11,30,31]. In this regard the European Organization for Research and Treatment of Cancer lymphoma group reported data from four consecutive controlled trials on patients with Hodgkin's disease clinically staged I–II and showed that it is possible to score ESHD patients to tailor therapy. In fact, the study demonstrated that in the favourable group the addition of chemotherapy to radiotherapy is not justified while it is mandatory for those patients who presented at diagnosis with unfavourable prognostic factors [10]. Conclusive data on the superiority of chemotherapy alone compared with radiotherapy for the treatment of ESHD patients with adverse prognostic factors are not available [20–22]. Pavlovsky *et al.* [26], in a randomised study in which cyclophosphamide, vinblastine, procarbazine and prednisone (CVPP) was compared with CVPP plus radiotherapy delivered to involved areas in 277 ESHD patients, reported that those with unfavourable prognosis treated with CVPP alone had a significantly lower probability of DFS (34% vs. 75%).

TOXICITY

Since high cure rates are already achieved in ESHD patients, the major objective in planning new treatments is to decrease toxicity without compromising outcome. Curative radiotherapy may impair muscle and bone growth and is associated with

Table 1. Clinical characteristics and response to treatment of 256 ESHD patients treated with chemotherapy alone

Ref.	Treatment	No. of patients	Stage	CR	% DFS (8–10 yrs)	% OS (8–10 yrs)	No. of relapses	Early relapses	True relapses
Paediatric									
18	MOPP	10	I–II (PS)	10	NA	NA	1	1	1
19	MVOPP	11	I–II	11	100	90	0	0	0
17	MOPP	11	I–II (CS)	11	NA	72	2	1	NA
45% paediatric/ 55% adult									
23	CVPP	142	I–II (CS)	121	62	82	25	NA	18
Adult									
24	MOPP	15	I–II (PS)	12	NA	NA	3	0	NA
20	MOPP	44	I–II (PS)	40	72.7	88	11	10	7
25	MOPP	9	I–II (PS)	8	67	89	2	2	NA
26	MOPP	14	I–II (CS)	13	93	93	0	0	0
Total		256		226 (88%)	62–100	72–93	44 (19%)	14 (74%)*	26 (84%)†

Percentage value calculated on *19 and †31 patients with data on early and true relapse.
CS = clinical stage, PS = pathological stage. NA = not available.

thyroid, pulmonary and heart dysfunction, as well as with secondary solid tumours. Moreover, if radiotherapy is done after laparotomy and splenectomy for staging there may be some morbidity and mortality related to these procedures. On the other hand, chemotherapy may be associated with nausea, vomiting and hair loss. MOPP or MOPP-related regimens induce sterility in most pubertal patients and nearly all adult men and older premenopausal women. Moreover, when used alone chemotherapy has a higher risk of secondary leukaemia than radiotherapy, while the risk of secondary solid tumours is similar or even less. Toxicity may be increased when both modalities are combined. Because of the induction of sterility, MOPP or related regimens cannot be recommended as sole treatment for ESHD. On the other hand ABVD or related regimens might be appropriate since they can achieve similar cure rates to MOPP, but with less risk of sterility and of secondary leukaemia [32]. To minimise the morbidity of MOPP and ABVD, Horning *et al.* studied chemotherapy with vinblastine, bleomycin and methotrexate (VBM) after involved-field radiotherapy in the treatment of favourable ESHD. Significantly better DFS was achieved with little adverse effect on fertility [33]. However, before considering VBM as sole treatment for ESHD, efficiency similar to that of MOPP or ABVD would need to be demonstrated.

CONCLUSIONS

Chemotherapy alone can achieve similar results to radiotherapy in ESHD. Thus chemotherapy might be a realistic option for those institutions in which effective radiotherapy equipment is not available. In paediatric Hodgkin's disease, chemotherapy alone compares favourably with combined modality treatment without adverse affects on muscle and bone growth.

However, when available, radiotherapy remains the treatment of choice for all other cases of ESHD with favourable prognostic factors since it achieves better local control and induces fewer side-effects. In addition patients who relapse after radiotherapy are more effectively salvaged by further treatment.

In ESHD patients with unfavourable prognostic features combined treatment might be preferable to chemotherapy alone. However, further studies will be necessary to clarify this and to establish the most effective form of chemotherapy.

Giuseppe Cimino
Haematology
Department of Human Biopathology
Università "La Sapienza"
Via Benevento 6
00161 Rome, Italy

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