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COMBINATION CHEMOTHERAPY AND RADIOTHERAPY IN NON-HODGKIN'S LYMPHOMATA

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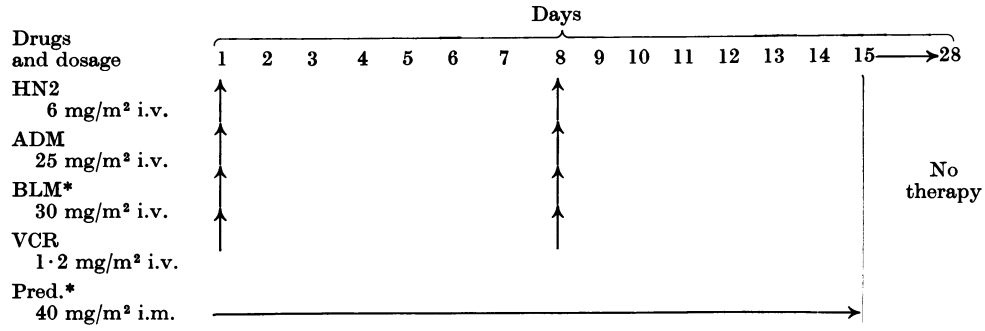
Summary.—The results obtained with intensive chemotherapy and intensive chemotherapy plus radiotherapy in non-Hodgkin's lymphomata are reported. A quintuple drug regimen (mechloretamine, adriamycin, bleomycin, vincristine and prednisone) in histiocytic lymphomata (Stage III and IV) yielded complete remissions in 53% and complete plus partial remissions in 77%. These figures were 44% and 64% respectively in lymphocytic lymphoma. In Stage III complete responders after combination chemotherapy were subsequently irradiated (involved field irradiation). The median duration of complete remission after completion of radiotherapy was 9·5 months in histiocytic and 12·0 months in lymphocytic lymphomata. At 2 years actuarial survival in Stage III and IV was better in patients with the lymphocytic type and with nodular pattern than with histiocytic and diffuse patterns. A more recent trial compares, in Stage IV patients, cyclophosphamide, vincristine and prednisone (CVP) *versus* adriamycin, bleomycin and prednisone (ABP). Although the number of evaluable patients is still limited, there appears to be no difference in the response rate between CVP and ABP. In Stages I and II, 6 cycles of CVP were given as adjuvant treatment after radiotherapy. At the present moment, there is no statistical difference in the relapse rate between the group of patients treated with radiotherapy alone and that with radiotherapy plus CVP.

A LARGE experience achieved in more than 25 years has shown that many growth inhibiting compounds are definitely active in non-Hodgkin's lymphomata (Carbone and Spurr, 1968; Carbone, 1972; Livingstone and Carter, 1970). The overall response rate to the different anticancer drugs is somewhat different in lymphocytic and in histiocytic lymphomata. Cyclophosphamide (CTX), mechloretamine (HN2), prednisone and imidazole carboxamide (DTIC) seem to be more active in the lymphocytic type; vincristine (VCR), adriamycin (doxorubicin) (ADM) and BCNU in histiocytic lymphoma. From the available data, bleomycin (BLM) appears to be equally effective in both lymphocytic and histiocytic lymphoma (Bonadonna *et al.*, 1972). With any given drug, complete remissions are usually observed in less than 30% of patients (Jones *et al.*, 1972; Livingstone and Carter, 1970).

In a retrospective analysis carried out in our Institute (Monfardini *et al.*, 1973) the median survival in all non-Hodgkin's lymphomata with diffuse extranodal disease and treated with single agent chemotherapy given in sequence was 16·2 months (nodular pattern 23·4 months, diffuse pattern 17·4 months). There is recent evidence that combination chemotherapy in advanced non-Hodgkin's lymphomata (Stages III and IV) can produce a higher percentage of complete responders followed by an increased survival, in comparison with single agent chemotherapy (Carbone, 1972; Luce *et al.*, 1971). Different types of combination chemotherapy have been tried but none so far can yet be considered the combination of choice as, for instance, MOPP is in Hodgkin's disease.

The aim of the present report is to summarize the results obtained in advanced non-Hodgkin's lymphomata with

TABLE I.—*Outline of 5-Drug Combination (Induction Phase)*



* On cycles 1, 3 and 5 for patients receiving 6 cycles; on cycles 1 and 2 for patients receiving 2 cycles.

clinical trials carried out during the past 3 years at the National Cancer Institute of Milan.

PATIENTS AND METHODS

From January 1971 to September 1972, a 5-drug regimen with HN2, ADM, BLM, VCR and prednisone (MABOP), as shown in Table I, was tried in histiocytic and lymphocytic lymphomata with Stages III and IV. Stage IV disease was determined through positive tissue samples (laparotomy, peritoneoscopy, bone marrow aspiration or biopsy). After staging evaluation, patients were randomized to receive either 6 or 2 cycles of MABOP (induction phase) with an appropriate dose reduction schedule in the presence of toxic manifestations. Patients with Stage IV disease in complete (CR) or partial (PR $>$ 50% response) remission were further randomized to receive a cyclical sequential maintenance treatment or maintenance treatment plus reinforcement. Maintenance therapy was carried out by rotating every 3 weeks CTX (90 mg/m^2 day), vinblastine (4 mg/m^2/week), procarbazine (90 mg/m/^{2} day) and methotrexate (10 mg/m^2 $\times$ 2/week). Reinforcement therapy administered between 2 maintenance cycles was carried out by one cycle of MABOP. Before and after reinforcement, there was a resting period of 4 weeks. Stage III patients in CR or PR after MABOP were subsequently irradiated with involved field or modified involved field cobalt therapy (3500–4500 rad). Patients in CR after radiotherapy were then randomized to receive no further therapy or maintenance plus reinforcement treatment.

Since a number of patients showed relapse during 6 cycles of MABOP as well as within a short period of time after subsequent radiation or during maintenance treatment, a second trial was started in October 1972. Two triple combinations (CVP and ABP) were tried in a prospective controlled study (Table II). The principal aim of this trial in Stage IV non-Hodgkin's lymphomata was to explore the therapeutic effects of 2 active non-cross resistant combinations which could possibly be used sequentially in subsequent studies. The first combination is represented by CVP, which was administered according to the dose schedule described by Bagley *et al.* (1972). The second combination (ABP) includes ADM administered in full dosage, BLM injected at half of the dosage employed in MABOP and prednisone given with the same dose schedule as in CVP. Both combinations were repeated every 3 weeks with a dose reduction schedule in presence of myelosuppression. Cross-over was carried out on relapse.

In Stage III disease, patients were randomized to receive radiotherapy, as described before, preceded or followed by 6 cycles of CVP. In Stage I and II disease we started a controlled adjuvant study which randomizes patients into 2 groups: radiotherapy alone *vs* radiotherapy followed after one month interval by 6 cycles of CVP.

The criteria for drug response were those of complete clinical remission, defined by complete disappearance of all signs and symptoms of disease for at least 1 month, including recalcification of bone metastases and negative bone marrow on a second aspirate and/or biopsy. The liver was rebiopsied in only few patients. Partial

TABLE II.—*Dose Schedule of CVP and ABP*

CVP	CTX	400 mg/m²/day × 5
	VCR	1·4 mg/m² on day 1
	Pred.	100 mg/m²/day × 5
ABP	ADM	75 mg/m² on day 1
	BLM	15 mg/m² on day 1 and 8
	Pred.	100 mg/m²/day × 5

CVP and ABP are repeated on Day 21 × 6 cycles

Stratification	1. Stage	(Clinical, pathological)
	2. Pattern	(Nodular, diffuse)
	3. Type	(Histiocytic, lymphocytic, mixed)

response was defined by a decrease of at least 50% in the sum of the products of the diameters of all lesions for a minimum of 4 weeks, without concomitant increase in size of any lesion or appearance of new lesions. No response was categorized by steady state or regression lesser than the partial remission. Relapse was defined by increase of about 50% in size of any measurable lesion, or the appearance of new lesions.

RESULTS

Response to MABOP

Table III reports the results in relation to histological type. In histiocytic lymphoma, there was no significant difference in terms of CR and CR + PR between the groups of patients given 6 or 2 cycles. On the other hand, in lymphocytic lymphoma 6 cycles of MABOP were much more effective (CR 64%) than 2 cycles (CR 18%). In histiocytic lymphoma 34% of patients showed relapse before the sixth cycle and in lymphocytic lymphoma 21%. The therapeutic response in relation to histological pattern showed no difference in terms of CR between nodular (58%) and diffuse (60%) pattern. In patients given 6 cycles, CR occurred in 57% of those with nodular and in 75% of those with diffuse pattern respectively. In patients given 2 cycles, these figures were 60% and 42% respectively. CR plus PR in relation to prior therapy (Table IV) showed that the lowest response occurred in patients previously treated with single agent chemotherapy, with the exception of lymphocytic lymphomata previously irradiated and treated with only 2 cycles of MABOP.

The median duration of response in Stage IV showed no statistical difference in histiocytic lymphomata, achieving CR after 6 (9 months) or 2 (7 months) cycles. The same observation applies to lymphocytic lymphomata (15 and 14 months respectively). In both types, partial responders showed a definitely shorter median duration (1–3·5 months) than complete responders, with the exception

TABLE III.—*Response to MABOP in Relation to Histological Type (Stages III and IV)*

	Histiocytic				Lymphocytic			
Schedule	Evaluable	CR	CR+ >50%	Relapse before 6th cycle	Evaluable	CR	CR+ >50%	Relapse before 6th cycle
6 cycles	29	16 (55%)	23 (79%)	10/29 (34%)	14	9 (64%)	12 (86%)	3/14 (21%)
2 cycles	28	14 (50%)	21 (75%)		11	2 (18%)	4 (36%)	
Total	57	30 (53%)	44 (77%)		25	11 (44%)	16 (64%)	

After the induction phase, Stages III–III$_S$ are subjected to RT, Stage IV to cyclic maintenance chemotherapy.

TABLE IV.—*Complete Plus Partial Remission in Relation to Prior Therapy (Stages III and IV after 6 and 2 Cycles)*

	Histological type		Histological pattern	
Prior therapy	Histiocytic (%)	Lymphocytic (%)	Nodular (%)	Diffuse (%)
None	92	82	86	85
Radiotherapy	70	50	75	65
Chemotherapy (± RT)	62	57	67	62

TABLE V.—*Response to MABOP in Histiocytic and Lymphocytic Lymphomata Followed by Radiotherapy (Stages III and III$_s$)*

	Response after MABOP					
Histological type	CR	>50%	CR after RT	Relapse during RT	Median duration of CR after RT	Median time from end of RT to relapse
Histiocytic	8/14 (57%)	3/14 (21%)	10/14 (71%)	1/11 (9%)	9·5 months (7–20)	7 months (7–12)
Lymphocytic	9/12 (75%)	2/12 (17%)	10/12 (83%)	1/11 (9%)	12·0 months (4–23)	7 months (4–10)

of those with lymphocytic lymphomata given 6 cycles (17·5 months). After 6 cycles the median duration of complete remission in patients with nodular lymphomata was longer (15 months) than in those with diffuse pattern (9 months). After 2 cycles these figures were 12 and 4·5 months respectively.

Table V reports the results obtained with chemotherapy followed by radiotherapy (RT) in Stage III patients. After radiation therapy, approximately the same percentage of patients with histiocytic and lymphocytic lymphoma were in CR, with the same number of patients relapsing during irradiation (9%). The median duration of CR after completion of radiotherapy was slightly higher in lymphocytic than in histiocytic lymphoma. However, the median time to relapse was the same in both types.

The actuarial analysis of survival in untreated Stage IV patients showed that at 2 years from initiation of treatment 67% of cases with lymphocytic lymphomata are alive *vs* 46% with histiocytic lymphoma. These figures were 86% and 67% respectively in patients with Stage III. In relation to histological pattern, survival data at 2 years were 61% (nodular) and 44% (diffuse) in Stage IV, and 100% (nodular) and 66% (diffuse) in Stage III. In both Stages III and IV survival in previously treated patients was definitely lower. However, patients with lymphocytic lymphomata and with the nodular pattern always showed a better survival in comparison with those with histiocytic and diffuse lymphoma.

Response to CVP and ABP

Table VI shows the response to primary and secondary therapy in Stage IV. Although the number of evaluable patients is still limited, there is not a significant difference in the therapeutic response after primary treatment between CVP and ABP in histiocytic (8/10 *vs* 7/8) and lymphocytic (2/3 *vs* 5/6) lymphoma. However, it should be noted that 3/8 patients treated with ABP showed relapse before the sixth cycle, compared with 1/10 given CVP. Secondary treatment (crossover after relapse) yielded only 1 CR in 5 evaluable patients. This was noted in a patient with histiocytic lymphoma treated with CVP. Due to the early stage of this trial, the median duration of response cannot be calculated.

Table VII summarizes the preliminary results obtained in Stage III. After radiotherapy as primary treatment (in-

TABLE VI.—*CVP and ABP in Stage IV, Response to Primary and Secondary Treatment*

	Combination	Therapy	Eval. cases	Response CR	Response PR>50%
Histiocytic	CVP	Primary	10	3	5
		Secondary	2/5	1	0
	ABP	Primary	8	2	5
		Secondary	1/2	0	0
Lymphocytic	CVP	Primary	3	2	0
		Secondary	2/2	0	0
	ABP	Primary	6	4	1
		Secondary	0		

TABLE VII—*Type and Duration of Response in Stages III–IIIs*

Sequence	Entered evaluable	CR during induction	Median duration*	Relapse during induction	Relapse during consolidation
RT → CVP	7/4	4/4	5·5 mo.	0/4	1/4
CVP → RT	7/6	4/6	3·5 mo.	2/6	0/4

* Calculated from the end of induction phase.

TABLE VIII.—*Adjuvant Combination Chemotherapy in Histiocytic and Lymphocytic Lymphomata (Stages I_E–I–II–II_E)*

Random	Stage	Evaluable	During RT	Relapse (months)* 0–1	1–3	3–6	6–12	12	Total
RT	Clinical†	7	0	0/7	1/7	1/6	0/5	0/2	2/7
	Pathological	16	1	2/15	1/13	1/10	0/7	0/4	5/16
	Total	23	1	2/22	2/20	2/16	0/12	0/6	7/23 (30%)
RT+ CVP	Clinical	5	0	0/5	1/4	0/3	1/2	—	2/5
	Pathological	18	2	0/16	0/15	0/11	0/8	0/3	2/18
	Total	23	2	0/21	1/19	0/14	1/10	0/3	4/23 (17%)

* Total/at risk

† Not determined with laparotomy but with bone marrow biopsy and peritoneoscopy.

duction), all patients achieved a complete remission and 1/4 relapsed during consolidation with CVP. On the other hand, only 4/6 patients treated initially with CVP achieved CR, with no relapse during subsequent irradiation.

The initial results of the adjuvant study in Stages I and II are reported in Table VIII. An equal number of patients is presently evaluable in each arm. Relapse (new manifestations of disease) during radiotherapy occurred in 3/46. New sites of involvement after radiotherapy occurred in all but one patient within 6 months from completion of irradiation. While we have noted so far an almost identical incidence in the relapse rate between clinical and pathological stages in patients treated with radiotherapy alone, in the group of patients treated also with CVP the incidence of new manifestations occurred mostly in patients not subjected to laparotomy. There is not yet a statistical difference in

TABLE IX.—*Manifestations of Toxicity after MABOP in Stages III–IIIs–IV Non-Hodgkin's Lymphomata*

	6 cycles		2 cycles	
	Untreated (19 cases) (%)	Prior therapy (10 cases) (%)	Untreated (13 cases) (%)	Prior therapy (24 cases) (%)
Leukopenia*	89	80	69	83
Thrombocytopenia†	58	80	—	17
Alopecia	95	100	92	83
Stomatitis	22	30	15	50
Cutaneous stria	42	50	38	25
Lung‡	16	1	—	—
Paraesthesiae	47	60	23	8
Gastric ulcer	—	1	—	—

* WBC $< 4000/mm^3$
† PLTS $< 150,000/mm^3$.
‡ Total BLM toxicity: 4/66 cases (6%)

the relapse rate between radiotherapy and radiotherapy plus CVP ($P < 0.05$). Furthermore, new lesions were noted to occur preferentially in diffuse (30%) rather than in nodular (12%) pattern. No difference was seen so far between histiocytic (24%) and lymphocytic (22%) types.

Toxicity

The side-effects after 6 and 2 cycles of MABOP are shown in Table IX. Haematopoietic toxicity (especially leukopenia) was the most prominent dose limiting factor. This required a temporary reduction in the dosage of myelosuppressive agents (HN2 and ADM). Bleomycin pulmonary toxicity, confirmed through repeated x-ray films, occurred in only patients given 6 cycles of MABOP. This side-effect was always detected at its early stage and upon prompt drug withdrawal it was reversible in all patients. Paresthesiae were observed especially in patients treated with 6 cycles, and in about 20% of cases the dose of VCR was temporarily reduced to 50%. There was only one fatality produced by chemotherapy. The patient, who is not included in the evaluable cases, showed an acute irreversible renal failure after the first dose of MABOP. The failure was secondary to hyperuricaemia produced by prompt disappearance of multiple adenopathies.

Toxicity after CVP and ABP in Stage IV can be summarized as follows: In patients given CVP leukopenia occurred in 94% of cases, thrombocytopenia in 59% and alopecia in 88%. In those given ABP these figures were 69%, 31% and 87% respectively. Neurotoxicity was noted in 7/17 patients treated with CVP; ECG changes in 1/16 treated with ABP. Death related to drug administration occurred in a total of 5/33 patients. Haemorrhage secondary to irreversible thrombocytopenia was noted in 2 patients (CVP 1 case, ABP 1 case). Irreversible leukopenia followed by septicaemia occurred in 3 patients (CVP 2 cases, ABP 1 case). CVP was, on the contrary, well tolerated in patients with Stage I, II and III, and despite temporary haematopoietic toxicity no fatalities attributable to combination chemotherapy were observed.

Toxicity after radiation therapy has been represented primarily by bone marrow depression. For the whole group pretreated with MABOP, the mean nadir of leucocyte counts was $2800/mm^3$ (range 1800–3200), the mean nadir of platelet counts was $50,000/mm^3$ (range 20,000–100,000). This required a temporary interruption of treatment, especially during the irradiation of retroperitoneal nodes. Radiation therapy was completed within a median of 8 weeks (range 4–16).

DISCUSSION

Non-Hodgkin's lymphomata represent a notoriously difficult group of diseases to maintain in complete remission for a long period of time with either radiotherapy or chemotherapy. The interpretation of published results is often impaired by the different criteria used in histopathology and staging classification. A number of retrospective analyses (Jones *et al.*, 1972; Monfardini *et al.*, 1973) have recently tried to relate the therapeutic response to the histopathological classification as described by Rappaport *et al.* (1956). The most important observations emerging from these studies indicate that the results of therapy depend on the cell type and on the histological pattern (diffuse or nodular). Trials are now carried out with radiotherapy, combination chemotherapy, or both, in clinical and pathological stages as well as in favourable and unfavourable histological variants.

Preliminary results of intensive chemotherapy have been reported to significantly increase the proportion of complete responders and the duration of the complete remission compared with single agents (Carbone, 1972; Livingstone and Carter, 1970). However, survival after combination chemotherapy and single agent chemotherapy administered in sequence has not yet been compared on a randomized basis in the different histological types.

The combinations tried so far in our Institute included adriamycin (doxorubicin) and bleomycin, since both compounds were found effective in non-Hodgkin's lymphomata during Phase II studies (Bonadonna *et al.*, 1972*a*, *b*). In particular, adriamycin was noted to be particularly effective in histiocytic lymphoma (overall response rate 88%). The therapeutic results in terms of complete remission after MABOP are in the range of those reported by other authors with different types of effective combinations. In our experience, there was not a significant difference in terms of response rate after 6 cycles of therapy between histiocytic and lymphocytic lymphomata, as well as between nodular and diffuse patterns. This fact could possibly be due also to the therapeutic effect of ADM. On the other hand, in previously untreated patients with either Stage III or IV disease, survival time at 2 years was better in lymphocytic and in nodular lymphomata than in histiocytic and diffuse lymphomata. After intensive chemotherapy, survival in Stage IV was also significantly improved for both histological types and patterns in a retrospective comparison with patients treated with single agent chemotherapy. Sufficient data are not yet available to state whether in Stage III and IV maintenance therapy, with or without periodic reinforcement, can be of any value.

The control of non-Hodgkin's lymphomata remains a difficult problem because of the considerable incidence of relapse during intensive therapy despite a significant improvement in the initial response rate. For this reason we are evaluating two different combinations such as CVP and ABP with the intent to employ them sequentially in future studies. Preliminary data show that both combinations appear equally effective in both histiocytic and lymphocytic lymphomata. Since, besides corticosteroids, both combinations include drugs with different mechanisms of action, it is conceivable that their appropriate use in sequence could yield an improved median duration of response.

The use of combination chemotherapy in association with radiotherapy in lymphomata apparently confined to the lymph nodes is still to be determined. The extent of radiation fields and the appropriate sequence with chemotherapy are problems which still await the results of large clinical trials. In patients with Stage I and II our results, as well as those of Jones *et al.* (1972), indicate that the relapse rate, especially in patients with diffuse histiocytic lymphoma, occur within the first 6 months from completion of involved field radiotherapy. Since most

new manifestations occur in extra-lymphatic sites, adjuvant chemotherapy appears indicated. However, from our initial results we do not have the evidence that CVP has decreased the relapse rate significantly.

In conclusion, the treatment of non-Hodgkin's lymphomata has improved during the past 5 years, primarily because of intensive cyclic chemotherapy and because of new agents. However, the progress in the control of this group of diseases has been, in general, slower than in Hodgkin's disease where extensive field high energy irradiation in early stages, and MOPP, or modifications of it, in advanced disease have produced appreciably improved long-term survival. The therapeutic improvement of non-Hodgkin's lymphomata appears strictly related to a better knowledge of their natural history. Staging laparotomy and identification of histologically favourable groups will probably be a step towards more successful control of the disease.

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