Results of Three Polychemotherapy Programs in Non-Hodgkin's Lymphomas

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A. Introduction

In the past 10 years, in spite of remarkable therapeutic progress with most hematological malignancies, non-Hodgkin's lymphoma (NHL) patients, particularly those with unfavorable histological types, remain a crux medicorum. Complete remissions are still comparatively rare and of short duration, and the disease is recurrent and progressive, with little hope of the cure so often observed in Hodgkin's disease.

Numerous salvage options based on "classical" cytostatics give variable results, and discrepancies between several published studies [1, 7, 8] may be explained at least partially by differences in patient characteristics, such as pathological type and clinical extent of non-Hodgkin's lymphoma.

Encouraged by the promising results of some investigators [3, 6, 10, 11, 16], we introduced in 156 cases three intensive multi-drug chemotherapy programs (CHOP or CHOP-Bleo, CHOMLA, CBVPM/AVBP; see Table 1) and now present the results.

B. Patients and Methods

Between 1979 and 1987, 156 patients with non-Hodgkin's lymphoma were treated at six hematological centers in Poland. All patients had a histological diagnosis of either intermediate (76 cases) or high-grade (80 cases) malignant lymphomas (Table 2).

Among 76 patients with intermediate-grade malignancy, 38 had large-cell lymphomas (31 diffuse and seven follicular), 24 had diffuse, small cleaved cell lymphomas, and 14 had diffuse mixed-cell lymphomas. Eighty patients classified as having high-grade malignancies were identified as follows: 33 cases, immunoblastic; 39, lymphoblastic, eight small, noncleaved cell lymphoma.[1] There were 95 men and 61 women with a median age of 46 years (range 18–65); 83 of these patients (31 in stage III and 52 in stage IV) had not received chemotherapy previously, and the remaining 73 patients (21 stage III and 52 stage IV) had been unsuccessfully treated with various chemotherapeutic regimens including COP, HCOP, LOP, MEV (A).

The extent of the disease was expressed in terms of criteria suggested at the Ann Arbor Conference [2] and included complete blood count with differential urinalysis, biochemical screening profile, serum protein electrophoresis, chest roentgenogram, and bone marrow aspiration or biopsy. In all patients a liver and spleen scan and abdominal ultrasonography were performed. In some patients, a CAT of the abdomen or a lymphanogiogram and spinal puncture for CSF cytology were done when the

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[1] In the present analysis the histology of lymph nodes was evaluated according to criteria of the Working Formulation of non-Hodgkin's lymphomas [15]

Table 1. Cytostatic programs

CHOP or CHOP-Bleo	
C – Cyclophosphamide	750 mg/m^2 i.v. on 1st day
H – Hydroxyrubicine	50 mg/m^2 i.v. on 1st day
O – Oncovine	1 mg/m^2 i.v. on 1st day
P – Prednisone	100 mg/m^2 p.o. on days 1–5
or	
B – Bleomycine	15 mg i.v. on 1st and 5th day
CHOMLA	
C – Cyclophosphamide	1000 mg i.v. on 4th day
H – Hydroxyurea p.o.	6 g/day/in 2 doses/on 1st and 7th day
O – Oncovine	1 mg i.v. on 2nd day
M – Methotrexate	120 mg i.v. on days 5, 10, and 15
L – Leucovorine	100 mg/in 4 doses/i.v. on days 6, 10, and 16
A – Adriblastine	40 mg/m^2 i.v. on 10th day
CBVPM/AVBP	
C – Cyclophosphamide	1200 mg/m^2 i.v. on 1st day
B – Bleomycine	13 mg i.m. on days 4–8
V – Vincristine	2 mg/m^2 (Max. dose 3 mg) i.v. on days 3 and 10
P – Prednisone	40 mg p.o. on days 4–17
M – Methotrexate	3 mg/kg i.v. on 20th day every 2 months
A – Adriblastine	30 mg/m^2 i.v. on days 2–4
V – Vincristine	1.4 mg/m^2 i.v. on days 1 and 8
B – Bleomycine	15 mg i.m. on days 2 and 8
P – Prednisone	40 mg p.o. on days 2–15 every 2 months

Table 2. Clinical and histological data

Program (no. of patients)		Histological grade of malignancy			
		Intermediate		High-grade	
		Previously		Previously	
		Untreated	treated	Untreated	treated
CHOP or CHOP-Bleo	(58)	20	10	18	10
CHOMLA	(46)	3	16	6	21
CBVPM/AVBP	(52)	20	7	16	9
Total	(156)	43	33	40	40
		76		80	

clinical presentation suggested possible involvement of the respective extranodal sites. Laparotomy was not routinely performed for staging purposes.

Patients were treated with three different chemotherapeutic regimens; CHOP or CHOP-Bleo (58 patients), CHOMLA (46 patients), and CBVPM/AVBP (52 patients) at the generally accepted doses of cytostatics included into these regimens [12–14]. Initial induction therapy with CHOP or CHOP-Bleo consisted of six cytostatic cycles, with CHOMLA of six to eight cycles, and with CBVPM/AVBP

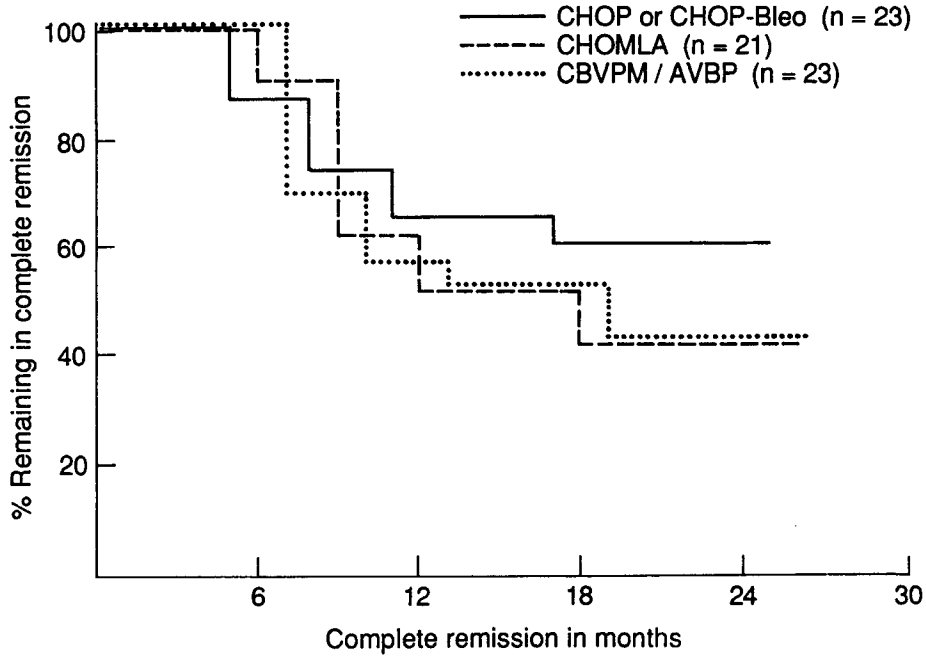

Fig. 1. Duration of complete remission for patients with intermediate and high-grade malignancy NHL. *Solid line* represents patients treated with CHOP or CHOP-Bleo, *broken line,* patients treated with CHOMLA, and *dotted line* patients treated with CBVPM/AVBP

Table 3. Results of treatment in all NHL patients

Program and number of patients		Evaluable patients (%)	Results of treatment (no. of patients) (%)		
			CR	PR	Failure or death
CHOP or		51	23	7	12 (23.5)
CHOP-Bleo	(58)	(88)	(45.0)	(13.7)	9 (17.6)
CHOMLA	(46)	40	21	6	3 (7.5)
		(87)	(52.5)	(15.0)	10 (25.0)
CBVPM/AVBP	(52)	47	23	11	9 (19.0)
		(90)	(48.9)	(23.0)	4 (8.0)
Total		138	67	24	24 (17.4)
		(88.5)	(48.5)	(17.4)	23 (16.6)
			91 (66.0)		

CR, Complete remission; PR, partial response

of four cycles each of the combined cytostatic regimen. After complete remission or partial response was achieved, two or three additional courses of the same cytostatics were given as consolidation. In some cases only adriamycin was omitted from the schedule when a total dose of 550 mg/m^2 had been reached.

After therapy (usually within 1–2 months after the last cycle of cytostatics) the patients were restaged again, particular attention being given to reassessing the initial involved site of the disease. Complete remission (CR) was defined as an absence of objective evidence of residual or subjective symptoms of persistent disease. Partial response (PR) required 50% reduction in tumor mass lasting at least 1 month.

Remission duration was ascertained from the date of the first objective complete remission to documented relapse. The data were analyzed by the life-table method [9], and differences among the curves were compared using the generalized Wilcoxon test modified by Gehan.

C. Results

One hundred thirty-eight (88.5%) of the 156 patients completed therapy and could be evaluated for response. Eighteen patients were not evaluable for response to therapy because of they did not complete follow-up. They were excluded from the survival curves.

Of the 138 evaluated patients, 67 (48.5%) achieved a complete remission and 24 (17.4%) a partial response (Table 3). Complete remissions were usually seen during induction cycles and at very similar rates (45%, 49% and 52.5%) after these three kinds of cytostatic regimens. Continuous CR in these three groups of treated patients has been documented in 42%–60% of patients.

The median disease-free survival for CHOP- or CHOP-Bleo-treated patients lasted 11.4 months and for those on the CHOMLA and CBVPM/AVBP programs 15 and 12.7 months respectively (Fig. 1).

The difference in the median disease-free survival between these three groups of patients was not statistically significant ($P=0.32$). There was no significant difference in the CR rate between the nontreated (37.2%) and the pretreated (38.2%) patients (Table 4).

Of all treated patients, 47 (34%) persons did not respond and 23 (16.6%) died within 4–11 months after starting therapy. The most common reasons for failure to achieve a complete response in these patients were persisting lymphadenopathy, bone marrow infiltration, and thrombocytopenic complications.

On evaluation of 138 patients under treatment in relation to the degree of ma-

Table 4. Results of chemotherapy in NHL patients who had received prior chemotherapy and in patients previously untreated

Program and past history of treatment (number of patients)			No. of evaluated patients	Response (no. of patients) (%)	
				CR	PR
CHOP or CHOP-Bleo	Untreated	(38)	51	19 (37.2)	5 (9.8)
	Refractory	(20)		4 (7.8)	2 (4.0)
CHOMLA	Untreated	(9)	40	7 (17.5)	1 (2.5)
	Refractory	(37)		14 (35.0)	5 (12.5)
CBVPM/AVBP	Untreated	(36)	47	18 (38.2)	1 (2.1)
	Refractory	(16)		5 (10.6)	10 (21.2)

CR, Complete remission; PR, partial response

Table 5. Results of chemotherapy according to grade of malignancy

Program and grade of malignancy (no. of patients)			No. of evaluable patients	Response (no. of patients) (%)	
				CR	PR
CHOP or CHOP-Bleo	Intermediate	(30)	28	12 (23.5)	5 (9.8)
	High	(28)	23	11 (21.5)	2 (4.0)
CHOMLA	Intermediate	(19)	18	12 (30.0)	2 (5.0)
	High	(27)	22	9 (22.5)	4 (22.5)
CBVPM/AVBP	Intermediate	(27)	23	5 (10.6)	9 (19.1)
	High	(25)	24	16 (38.2)	2 (4.2)

CR, Complete remission; PR, partial response

Table 6. Number of patients with NHL who relapsed after obtaining complete remission

Program (no. of patients)		Number of relapsing patients with NHL			
		to 3 months	to 6 months	to 12 months	above 12 months
CHOP or CHOP-Bleo	(28)	3	3	2	1
CHOMLA	(21)	2	6	2	2
CBVPM/AVBP	(23)	7	3	1	2

lignancy, it was found that the CBVPM/AVBP regimen was most effective in high-grade NHL (38.2% CR). In intermediate-grade NHL the best was the CHOMLA program (30% of CR, Table 5).

Approximately half of the patients who achieved an initial CR have relapsed within 3–15 months (Table 6). Relapse was most common at the previous site of involvement, i.e., lymph nodes (21 patients), spleen and liver (16 patients), and bone marrow (three patients).

D. Discussion

Although many agents are active in the treatment of NHL, only a few chemotherapy combinations have been shown to improve the survival of patients. The introduction of chemotherapy combinations containing adriamycin and bleomycin such as the CHOP and CHOP-Bleo regimens in particular represents an important advance in therapy. Several groups have reported plateaus in disease-free survival estimates, suggesting cure of 30%–35% of patients with intermediate or high-grade non-Hodgkin's lymphoma [4, 12, 14]. Unfortunately the majority of these patients do not achieve a plateau in *relapse*-free survival with CHOP or CHOP-Bleo or similar combination chemotherapy.

More recently, programs such as Pro-MACE-MOPP [5], COP-BLAM [11] M-BACOD [16], and MACOP-B [10] have achieved complete response rates of over 70% and appear to have extended the disease-free survival to more than 60%.

The results of treatment of our patients with three intensive and similar cytostatic programs were not satisfactory. Complete remissions were achieved in only 48.5% of all patients, and nearly half of these patients relapsed within 3–15 months after completing therapy.

Based on our experience with these three combined cytostatic programs, especially for resistant and relapsing NHL patients, a further modification of the present programs is necessary. But the real solution can be expected only with the introduction of potent new cytostatic drugs and the improvement of supportive care.

E. Conclusions

1. Of 138 advanced (clinical stage III or IV) NHL patients treated by three different cytostatic programs (CHOP or CHOP-Bleo, CHOMLA, CBVPM/AVBP), complete remission was obtained in 67 patients (48.5%) and partial response in 24 patients (17.4%).
2. Among the three cytostatic programs the highest rate of complete remission was observed after CHOMLA – 52.5%.
3. In untreated and high-grade malignant NHL patients the most effective cytostatic program was CBVPM/AVBP (38.2% complete remissions).
4. The results presented show that these three alternative chemotherapy programs are still only partly effective in the treatment of advanced intermediate and high-grade malignant NHL.

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