of 15 patients with advanced and relapsing non-Hodgkin lymphoma.

2. Treatment with the HCOLMA program brought complete remission only in 4 (23%) out of 17 patients.

3. In both groups of treated patients 6 (18.7%) died.

4. The CBVPM/AVBP regimen is more effective for patients with advanced and relapsing non-Hodgkin lymphoma, than HCOMLA, but survival curves for both groups of patients over 4 to 16 months of observation are similar.

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Preliminary Results with an Alternating Combination in Non-Hodgkin's Malignant Lymphomas

GREEK LYMPHOMA RESEARCH GROUP

INTRODUCTION

Cure of malignant non-Hodgkin's lymphomas (NHL) can be achieved in a significant percentage of previously untreated patients.

This is true for high grade lymphomas while the intermediate grade ones have a much lower cure rate [3]. In order to further improve results, several investigators have tried new combinations and recently alternating or sequential combinations [1].

The percentage of remissions has increased significantly with some of these combinations but toxicity is considerable.

In an attempt to reduce toxicity without decreasing effectiveness, we have used an alternating schedule of drugs which have been effective both as single agents and as combinations for the treatment of intermediate and high grade NHL. We also included the intermediate grade NHL lymphomas because in spite of their better prognosis the cure rate is relatively low.

MATERIAL AND METHODS

Thirty-four previously untreated patients entered the protocol. Twenty were males and 14 females with an age range of 22 to 70 years (mean age 53.85).

Twenty-two patients had high and 12 intermediate grade lymphomas. Histologic classification was done according to the New Working Formulation. The clinical stage of the patients was as follows: Stage I:2, II:12, III:4, IV:16 patients. Staging proce-

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dures included careful clinical examination, complete hematologic and biochemical profile, bone marrow biopsy, radiologic survey, CT scan and, when indicated, liver biopsy. The bone marrow was infiltrated in 10 out of 32 patients examined. The performance status of the patients when entering the protocol was 0 or 1 in twenty-nine and 2 or 3 in five.

Treatment schedule (PEV/M-L-B-CHOP): Day 1: cisplatin 60 mg/m² and vindesine 3 mg/m² (maximum 5 mg); days 1, 2, and 3: etoposide 120 mg/m² I.V.; day 14 methotrexate 500 mg (200 I.V. bolus and 300 mg drip over 6 hours); days 15, 16, 17: leucovorin 15 mg every 6 hours for eight to twelve doses; day 28 B-CHOP (bleomycin 15 mg, cyclophosphamide 800 mg/m², adriamycin 50 mg/m², vincristine 2 mg and prednisone 100 mg/m² daily for five days).

The course was repeated every 49 days.

Two courses were given after achieving complete remission with a minimum total of six courses.

Complete blood counts, platelets, blood urea and creatinine were done before each course of treatment. Other biochemical test, x-rays, bone marrow biopsies and CT scans were repeated at various intervals as indicated.

RESULTS

Nine patients received fewer than 2 courses, six 2 courses and the remaining nineteen, from 3 to 6 courses. One patient developed deep jaundice after receiving the first part of the course and could not continue with methotrexate. Therefore he was withdrawn from the protocol. Thirty-two of the 33 evaluable patients achieved complete or partial remissions *(Table 1)*. Eighteen had complete remission (54.5%) and 14 partial (42.4%). Seven of the patients in partial remission have so far received 2 or less courses.

Two patients died of septicemia while in partial remission. Two other patients relapsed 4 and 8 months after a partial or complete remission respectively. The patient in complete remission who relapsed had refused treatment after 2 $^1/_2$ courses and relapsed 4 months after discontinuing treatment. The remaining 29 patients continue to be in partial or complete remission *(Figure 1)*.

TABLE 1 - *Response and relapse rates according to histology*

Response	HG	IG	Total
Complete remission	13	5	18 (54.5%)
Partial remission	8	6	14 (42.4%)
No response	0	1	1
Non-evaluable	1	0	1
No of patients	22	12	34
Relapses	2	—	2 (6.2%)

HG = High grade NHL.
IG = Intermediate grade.

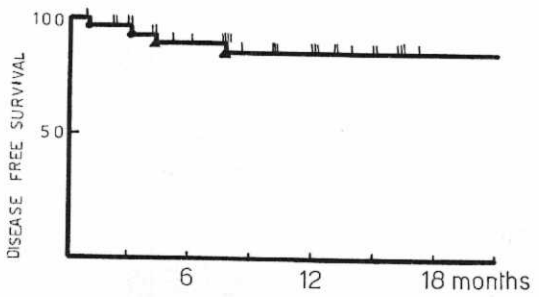

Figure 1 - Disease free actuarial survival of responding patients. ▲ Relapse, • death due to sepsis.

TOXICITY

Two patients in partial remission died of septicemia due to severe myelotoxicity. One of them immediately after completion, of the B-CHOP of the second course and the other after the first methotrexate infusion. This patient also developed severe renal and gastrointestinal toxicity. Another twelve patients developed mild to severe myelotoxicity (in 4 severe). Of the 10 patients with bone marrow infiltration 7 had mild to severe myelotoxicity, including the 2 who died of septicemia. Of the 22 patients without bone marrow infiltration only 7 had myelotoxicity which was severe in 2.

Mild to moderate neurotoxicity was present in 3 patients, renal toxicity was absent. Nausea and vomitting was present in almost all patients and was severe in some of them.

DISCUSSION

The results of this study are encouraging despite the two unexpected deaths. The overall remission rate of 96.9% compares favorably with published results to date[1,2] using alternating or sequential combinations. However, it should be taken into consideration that many of our patients have a short follow-up period or are still under treatment. The response rate for high and intermediate grade NHL is comparable. Patients of stages I and II have a higher complete remission rate than patients of stages III and IV. However, because of the small numbers the difference is not statisticaly significant.

Toxicity, although significant, seems to be

milder than that reported for other chemotherapeutic combinations with similar high remission rates. Infiltration of bone marrow predisposes to myelotoxicity and perhaps the doses of drugs should be reduced during the first courses if the infiltration is heavy.

It is concluded that this alternating chemotherapy schedule is higly effective for the treatment of intermediate and high grade NHL. It remains to be seen whether the remissions achieved will be long-lasting.

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Treatment of Resistant Non-Hodgkin's Lymphomas with Cisplatin, Etoposide, Vindesine, Methotrexate with Leucovorin Rescue

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INTRODUCTION

It is known that patients with non-Hodgkin's lymphomas (NHL) of intermediate or high-grade malignancy may relapse after first-line chemotherapy and/or radiotherapy or may not achieve a remission at all in 50-60% of the cases [1,3]. For these patients, various combinations are used either empirically or based on cell kinetics, but the results are usually not very successful, especially on a long-term basis [2].

We devised a combination of cis-platinum, etoposide, and vindesine followed by intermediate doses of methotrexate and leucovorin rescue, because these agents were found to be active as single agents in non-Hodgkin's lymphomas.

The aim of this study was to evaluate activity of this combination in resistant and relapsing patients and also to evaluate degree of toxicity. The study was initiated as a pilot study with the aim of using the combination if acceptable for activity and toxicity, as the one arm of an alternating schedule.

MATERIAL AND METHODS

Twenty-two patients, 10 males and 12 females, with an age range from 15 to 67 years, entered the trial from June, 1983 to December, 1984.

Sixteen patients had high-grade and 6 intermediate-grade malignancy NHL. Of the patients with high-grade malignancy NHL, 6 had immunoblastic lymphoma. The histologic classification used was that of the New Working Formulation.

The clinical stage of the patients was as follows: IIA: 1, IIB: 2, IIIA: 1, IIIB: 3, IVA: 8, and IVB: 7 patients.

Staging procedures included careful clinical ex-

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