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

GREEK LYMPHOMA RESEARCH GROUP *

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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TABLE 1 - *Response rate according to histology*

Response	HG	IG	Total
Complete remission	2 (19+, 20+ m)	0	11%
Partial remission	4 (1-9 m)	1 (3 m)	28%
No response	6	5	61%
Non-evaluable	4	0	
No. of patients	16	6	

HG: High-grade NHL.
IG: Intermediate-grade NHL.

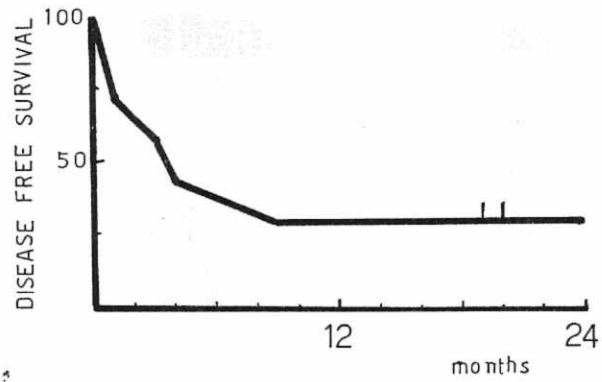

Figure 1 - Disease-free actuarial survival of responding patients.

amination, complete hematologic and biochemical profile, and in most of them, radiologic survey, CT scan, and bone marrow biospy.

Bone marrow was infiltrated in 3 of 19 patients examined. Five patients had skin infiltration. All patients were previously treated either with chemotherapy alone or in combination with irradiation. The response to previous treatment of these patients was as follows: Complete remission 11, partial remission 6, and no response 2.

In 2 patients there was insufficient information for response. The performance status of the patients when entering the protocol was: 0: 5 patients, 1: 10 patients, 2: 4 patients and 3+4: 3 patients.

Treatment schedule (PEV/M-L): Day 1 - cisplatin 60 mg/m², vindesine 3 mg/m². Days 1, 2, 3 - etoposide 120 mg/m² i.v. Day 14 - methotrexate 500 mg i.v. drip over 6 hours. Days 15, 16, 17 - leucovorin 15 mg every 6 hours.

The course was repeated every 28 days.

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

RESULTS

Thirteen patients received less than 2 courses of treatment, 4 received 2 courses, and the rest from 3 to 9 courses. Four of the patients are not evaluable for response; one died of myocardial infarction immediately after completion of the first course and 3 refused further treatment. Of the remaining 18 patients, 2 achieved complete remission which continues after 19+ and 20+ months, 5 achieved partial remission of 1 to 9 months' duration, and the remaining had either no response or progressive disease or died from side effects of the treatment (*Figure 1*).

Eleven patients who had no response or had progressive disease were withdrawn from the protocol and had other types of treatment. Of those who died, 3 died from septicemia due to myelotoxicity, 1 from progressive disease (performance status 4), and 1 of acute respiratory distress despite achieving a partial remission after the first course.

TOXICITY

Six patients had severe myelotoxicity involving mainly the granulocytes and, to a lesser degree, erythrocytes and platelets. Another 2 patients had moderate granulocytopenia.

One patient had severe nephrotoxicity and one moderate neurotoxicity. The latter is in complete remission and has no neurologic deficit.

DISCUSSION

Treatment of resistant NHL of intermediate- or high-grade malignancy is usually unrewarding.

Many combinations have been tried, but the results are either unsatisfactory or of short duration. Most investigators report a response rate of 30-60% with duration of response of 3 to 13 months [2]. Some of the combinations tested use either cisplatin or one of the epipodophylotoxins.

We used in the past a combination of cisplatin, VM-26, and hexametylmelanine in a few patients with NHL and we achieved a remission rate of 28.5%. Most of these remissions were short-lived.

In this trial the combination of PEV/M-L appears more promising. The response rate of 39% with 11% complete, lasting remissions in heavily pre-treated patients is encouraging.

It is worth mentioning that of the 6 patients with immunoblastic lymphoma, 2 had complete and 2 partial remission. It is conceivable that after treating more patients, this histologic subgroup may emerge to be more sensitive to these drugs.

Myelotoxicity was moderate to severe, partially

attributable to poor bone marrow reserves due either to heavy previous chemo/radiotherapy or to marrow infiltration. Nephrotoxicity and neurotoxicity was mild. Because of the encouraging results, we decided to continue this trial and use PEV/M-L as a standard second-line treatment especially for the immunoblastic NHL.

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Treatment of Poor Prognosis Acute Myeloid Leukemia with Aggressive and Non-Aggressive Chemotherapy

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With the development of modern chemotherapy protocols, in combination with greatly improved supportive care, a majority of adult patients with acute myeloid leukemia (AML) today achieve a complete remission (CR). Bone marrow transplantation has offered a new possibility of prolonged remission and even cure to an increasing number of younger patients with compatible donors, but most AML patients still relapse and only a small minority are actually cured. Attempts have been made to identify poor prognostic features and to try other treatment modalities for these patients. Some of the most significant disadvantageous factors for achieving CR or long survival include: high age, secondary leukemia or leukemia developing from a myelodysplastic syndrome (MDS), abundance of chromosomal abnormalities, abnormal growth pattern *in vitro* with excessive cluster formation, difficulties or failure to achieve CR, and early relapse.

With the development of ablative cytotoxic therapy in combination with bone marrow transplantation (BMT) from an HLA-matched donor, improved treatment results have been reported. Long-time survivors (possibly cures) approaching the 30% level are foiund in some studies. To widen the indications for excessively high-dose chemotherapy treatment and to avoid the risk of graft-versus-host disease, autologous bone marrow transplantation (ABMT) trials have been started. So far, these show encouraging results with, for example, a 5-year survival probability of 47% among patients transplanted in first CR in the collaborative EBMT Study Group (1986).

These promising reports have stimulated hematologists to treat poor prognosis AML patients (PPAML) with higher doses of cytotoxic drugs even without bone marrow transplantation. The most frequently used high-dose substance is cytosine arabinoside (ARA-C), often in combination with L-asparaginase, daunorubicin, amsacrine, 5-azacytidine, or mitoxantrone. These drugs have been used mainly for patients in early relapse or with refractory leuke-

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