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A phase-II study with idarubicin, etoposide and prednisone (IVPP), in patients with refractory or early relapsed intermediate or high grade non-Hodgkin's lymphoma

Sir,

Patients with non-Hodgkin's lymphoma (NHL) refractory to primary chemotherapy (CT) or relapse have an unfavorable prognosis. A variety of salvage protocols for such patients are available, and, overall, approximately 60% of all patients with relapsed or refractory disease can achieve complete remission (CR) or partial remission (PR) following reinduction.

Idarubicin is a new anthracycline derivative which when given as monotherapy or in combination with other agents, to either relapsed or refractory patients or previously untreated patients with NHL, has shown a considerable efficacy.[1-5]

The object of this prospective study was to determine whether a moderately intensive regimen comprising idarubicin, etoposide and prednisone (IVPP) is effective in relapsed or refractory patients with intermediate or high grade NHL.

Between March 1994 and September 1996, 18 consecutive patients with intermediate or high grade NHL were diagnosed and treated in our units.

Patients were eligible for the study if they had not reached CR or relapsed after front line treatment for their lymphoma. All patients had been previously treated according to the protocol of a randomized study with either CEOP (cyclophosphamide, epirubicin, vincristine, prednisone) or CNOP (novantrone instead of epirubicin). For various reasons, mainly age related, the patients included were not eligible for megatherapy. After first line treatment the disease remained resistant in 14 (78%) patients. In the other four patients, the disease recurred within 2-10 months after the induced CR has been achieved.

The treatment regimen under study consisted of idarubicin 10 mg/m^2 days 1-3 IV, etoposide 100 mg/m^2 days 1-3 IV, and prednisone 100 mg p.o. days 1-7 (IVPP regimen). A CR was defined as the clinical and X-ray disappearance of all detectable disease for a minimum of two months, without the appearance of any new lesion. A PR was defined as a 50% or greater reduction of the measurable lesions for at least one month. Responding patients (CR or PR) received six courses of treatment. Patients who developed progressive disease after one course or who failed to achieve at least a PR after two, were regarded as treatment failures and taken out of the study. All patients starting therapy were considered evaluable.

The characteristics of the patients participating in this study are summarized in Table 1.

Of the 18 patients, 4 received only one cycle of CT due to disease progression. Eight patients received 2-4 cycles and 6 patients 5-6 cycles. All courses of the IVPP regimen were given as in-patient therapy. Six patients (33%) responded: four achieved CR and two PR. Complete remission lasted 3 months in one patient and 16 months in another. One CR has now lasted 30 months and another 37 months so far. Of the four CR patients one had been resistant to front line treatment and 3 had relapsed early. Of the two patients who exhibited PR one was resistant and the other had relapsed early.

As far as concerns toxicity, all patients developed alopecia and 5 of them oral mucositis. Hematologic toxicity according to the WHO scale was as follows:

Table 1. Characteristics of the 18 patients with resistant or relapsed intermediate or high grade NHL.

Number of patients		18
Age (median-range)		63 (40-72)
Male/female		8/10
Histology		
Large cell		9
Immunoblastic		3
Follicular large cell		3
Mixed small and large cell		1
K1 anaplastic		1
T-peripheral		1
International Prognostic Index of NHL (6)	*At presentation*	*At the beginning of IVPP regimen*
Low	4	3
Low Intermediate	8	4
High Intermediate	4	9
High	2	2
Resistant to primary treatment		14
Early relapse (<12 months)		4

anemia was observed in 10/18 patients (7 grade 1-2 and 3 grade 3-4), neutropenia in 13/18 patients (5 grade 2 and 8 grade 3-4) and thrombocytopenia in 8/18 patients (4 grade 1-2 and 4 grade 3-4). Supportive treatment with G-CSF was given to 12 patients. Blood transfusions were given to patients with grade 3-4 anemia, while platelet transfusion was used in only one case with bone marrow involvement.

The prognosis of patients with NHL who have relapsed or were resistant to front line treatment remains poor. Several conventional salvage protocols are available for such patients.[1-4,7,8] Overall response rates (CR+PR) of up to 60% have been reported, depending on the characteristics of the patients included i.e. age, primary resistance, early or late relapse. The prognosis is particularly dismal for elderly patients or those with primary refractory disease.

Idarubicin is an interesting agent whose use in the treatment of NHL is worth investigation.[9] Idarubicin was initially tested as monotherapy in patients with relapsed or refractory disease[1] to confirm its activity. Next it was combined with other agents with known activity either in relapsed or refractory patients or as a first line treatment, often used in place of doxorubicin.[2-5] In relapsed or refractory disease the response rates to idarubicin-containing regimens are up to 60%.[2,3]

This study included 18 patients with unfavorable prognosis according to the international index[6] and the majority of them (14/18) exhibited resistance to front line treatment. The response rate was 33% which is lower than that obtained in other studies.[3] The lower remission rate in the present study can be attributed to the unfavorable clinical characteristics of the patients.

Hematotoxicity, mainly neutropenia, was common with this regimen, but no toxic death occurred. Supportive treatment with G-CSF was used in the majority of patients.

In summary the IVPP regimen was effective in some relapsed or refractory patients with intermediate or high grade NHL and unfavorable clinical characteristics. It may be an alternative treatment for elderly or other patients not eligible for intensive regimens.

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Genetic polymorphism of methylenetetrahydrofolate reductase and venous thromboembolism: a case-control study

Sir,

Moderately high total plasma homocysteine (Hcy) levels have been demonstrated to be an independent risk factor for arterial and venous diseases.[1,2] This situation can result from genetic defects and folate, B6, B12 vitamin deficiencies.[3] Recently, a point mutation (C677T) in the gene encoding methylenetetrahydrofolate reductase (MTHFR), a key enzyme involved in Hcy remethylation, has been reported by Frosst *et al*.[4] This polymorphism in the homozygous variant (TT genotype) was associated with increased enzymatic thermolability and consequently, was involved in some cases of hyperhomocysteinemia, especially in fasting conditions, when folate intake is low. In some reports about coronary heart disease, the risk was elevated in the homozygous variant, but in anothers did not.[5] In venous thromboembolism, moderate hyperhomocysteinemia has also been found to be a significant risk factor,[6] but the MTHFR genetic condition is