NEWER CHEMOTHERAPY STRATEGIES IN PATIENTS WITH REFRACTORY NON-HODGKIN'S LYMPHOMA

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SUMMARY

This report centres upon the evolution of chemotherapeutic programmes employed over the years in combination with other therapeutic modalities in the management of advanced non-Hodgkin's lymphoma which can be counted among the most chemo and radio-sensitive tumors that are encountered in clinical practice. The evolutionary sequence leading to our present concept in the therapy of non-Hodgkin's lymphoma has passed through several stages.

An extensive review of this progressive change in therapeutic concepts is beyond the scope of this paper. Because of the changes that have taken place over the past five decades, there has been a dramatic improvement in survival of the patients with advanced non-Hodgkin's lymphoma.

At present, the treatment of choice for early non-Hodgkin's lymphoma remains radiation therapy. However, strong consideration is now given to adding poly-drug chemotherapy to the management of these patients in the hope of preventing late recurrence outside the irradiated areas. In contrast, the basic approach to the treatment of advanced non-Hodgkin's lymphoma is to use poly drug chemotherapy programmes. Radiation therapy may be used to treat areas of refractory disease or in a prophylactic manner to areas of greatest original tumor volume in the hope of sterilizing residual foci of cancer cells. Although extended field radiation therapy is unquestionably superior to local irradiation in the management of stage-III non-Hodgkin's lymphoma; when used alone, it has proved a disappointing approach in achieving tumor control.

The introduction of CHOP combination represented a dramatic advance in the treatment of patients with advanced non-Hodgkin's lymphoma. They achieved an 80% complete remission rate. The complete remission rate in our patients with CHOP was at the lower end of those reported in the literature. In an attempt to improve upon the results, we have designed a new treatment programme using two different strategies. The first is a totally new potentially non-cross resistant drug combination (C.E.P.P.) i.e. Cyclo-phosphamide, Etoposide, Cisplatinium and Depo-medrol (Table 1). The second is the use of adjunctive moderate dose radiation therapy to areas intitally involved with bulky nodal disease which would be likely sites of relapse after chemotherapy alone. We present a brief update of this programme which has not been previously reported else-where.[1,2,5]

MATERIAL AND METHODS

Between January 1989 and April 1991, a total of 13 patients (10 males and 3 females) with advanced refractory non-Hodgkin's lymphoma were entered into this combined treatment programme. Their age ranged from 22 - 68 years.

Table 1

4-DRUGS COMBINATION CHEMOTHERAPY REGIMEN (CEPP)

Drugs	Dosage Schedule	Route of Administration	Interval	No. of cycles
Inj. Cyclophosphamide	300 Mg/m2	I/v Day 1-3	4 Wks.	7-8 Cycles
Inj. Etoposide (VP-16)	100 Mg/m2	1/v " "	4 Wks.	" " "
Inj. Cisplatinum	20 Mg/m2	I/v " "	4 Wks.	" " "
Inj. Depo-Medrol (Long Acting Prednisolone)	60 Mg/m2	I/m " "	4 Wks.	" " "

N.B. (Dosage adjusted according to blood picture and general condition).

Majority of the patients were previously treated with multi-drug chemotherapy, receiving 3-6 cycles of CHOP regimen. They had stage II-IV disease, mostly with stage B symptoms and bone-marrow involvement. Histologically, most of them had high grade lymphoma. and few with refractory intermadiate grade lymphoma. All patients had the following pre-treatment investigations i.e. C.B.C, X-ray chest, LFT, blood urea, creatinine, urine analysis and liver scan. Skeletal X-ray, bone and brain scans were done as needed and further evaluation of patients was made at 4 week intervals.

All patients received 3-days courses of 4-drugs combination chemotherapy regimen at 4 weeks interval, utilizing cylophophamide 300 mg/m^2 IV, Etoposide (VP-16) 100 mg/m^2 IV, cisplatinium 20 mg/m^2 IV and Depo-medrol (long acting prednisolone) 60 mg/m^2 IM. The drugs were administered by IV drip infusion (Normal Saline).

After 4 courses of chemotherapy, an involved field irradiation with a tumor dose of 30-35 grays in three and half weeks time was employed, using cobalt-60 to areas of initial bulky (more than 5 cm^2) nodal disease followed after 2 wks rest period by 3 additional courses of C.E.P.P. chemotherapy.

RESULTS

With this combined approach, we have achieved very encouraging results. Complete response (C.R.), defined as a total disappearance of all subjective and objective findings attributable to the under-lying disease, was noticed in 82% and partial response (P.R) with more than 50% reduction of measurable lesion was achieved in 11% cases and one patient it was too early to evaluate. The over-all response was 93% and no patient failed to repond. The response was less marked in patients with stage IV lymphoblastic lymphoma, having meningeal infiltration. The median

duration of remission was approximately 15 months. The best results were obtained in patients in whom the first complete remission lasted for more than 6 months.

Toxicity

Our experience with toxicity in this group of 13-patients is shown in Table-2. Most of the patients tolerated the treatment well. Nausea and vomiting was noticed in nearly all the patients, related to the administration of Cisplatinium and Etoposide. Anti-emetics were helpful in minimizing but not preventing nausea and vomiting. We also noticed signs of bone marrow depression in the form of transient leukopenia, thrombocytopenia and anaemia, particularly in patients with marrow involvement but were reversible. Alopecia was noticed in a few patients but was always reversible.

DISCUSSION

The introduction of CHOP combination has dramatically improved the out-look for patients with advanced non-Hodgkin's, lymphoma. But inspite of the success of CHOP, more than 50-60% of the patients treated with this regimen fail to be cured. The majority of patients treated with 6 cycles of CHOP relapsed with-in 1-2 years time span. As a consequence of this, a variety of competing poly-drug regimen have been proposed such as adding Bleomycin, CCNU, Etoposide and so on but none of these combinations have shown any real advantage over the CHOP regimen. Currently, there are no standard salvage therapies (including bone marrow trans-plantation) for refractory aggressive lymphoma. But during the last 10 years, important advances have taken place and resulted in high cure fraction. These innovations can be divided into two major areas.[1] The increased understanding of the natural history and prognostic factors of various cell types which enable us to identify before hand high risk patients so that their therapy can be modified accordingly.[2] The introduction of new drugs and regimens that allow us not only to rescue some patients who have failed therapy but also to improve the results of front-line therapy. Since we wished to improve upon our results in patients with refractory non-Hodgkin's lymphoma, we made two major modifications. The first was to replace the classic CHOP combination chemotherapy scheme with a potentially non-cross resistant combination of drug (C.E.P.P). The second modification was the use of adjuvant moderate dose irradiation administered to nodal sites initially involved with bulky disease. These were areas where relapse was found to be most frequent in patients treated with chemotherapy alone. The results of this study demonstrate that this combined modality treatment produces high complete remission rates and more then half of these patients achieve long term disease free survival. More than one remission may be obtained by repeated administration of the same combination regimen.[3,4,6,7,10]

CONCLUSION

In this report, I have presented our experience with a limited number of patients over a short period of nearly two and half years. I sincerely believe that this combined approach, using a totally new combination of non-cross resistant drugs with adjuvant moderate dose irradiation, is without question useful in the treatment of patients with refractory non-Hodgkin's lymphoma and offers better survival and improved quality of life. Patients can expect not only manyyears of freedom from

Table 2.

TOXICITY

Side Effects	No. of Cases	%
A. G.I. Tract		
Nausea & vomiting	13	100%
B. Haematological		
i) Anaemia		
HB < 10 Gram/dl	10	77%
ii) Leukopenia		
WBC < 3500/cmm	10	77%
iii) Thrombocytopenia		

consequences of disseminated disease but also the hope of a cure but it is too early to conclude that the long term results will be equally good.

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