Original Articles

CHEMOTHERAPY IN HODGKIN'S DISEASE

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Objective: *To assess the efficacy of primary chemotherapy in patients with clinically staged Hodgkin's disease.* ***Design:*** *Non randomized study.* ***Setting:*** *Pediatric Oncology Division of Regional Cancer Center.* ***Subjects:*** *Twenty nine children with Hodgkin's disease.* ***Interventions:*** *Chemotherapy was given to 21 patients whose parents agreed for the same. Sixteen children received COPP regimen and 5 received MOPP regimen.* ***Results:*** *Complete remission was achieved in 19 patients. The relapse free survival and overall survival in these patients were 76% and 86%, respectively at 5 years. There was no death related to chemotherapy toxicity.* ***Conclusion:*** *Combination chemotherapy is an effective modality of treatment for children with Hodgkin's disease.*

Key words: *Hodgkin's disease, Chemotherapy.*

PROGNOSIS in children with Hodgkin's Disease (HD) has steadily improved over the last 3 decades to become an ideal model where one can achieve high cure rates. The use of multiagent chemotherapy and radiotherapy had markedly improved the relapse free survival (RFS) and overall survival for children with HD(1). In an effort to maximize survival and minimize treatment related complications, various methods for treating children with HD have been reported. Some investigators use involved field radiation (IF XRT) alone in early stages, while others have advocated the use of chemotherapy and low dose irradiation regardless of initial stage in order to avoid the risk of growth retardation and staging laparotomy. In order to eliminate the marked growth disturbance following extended field irradiation and to avoid staging laparotomy, we have taken a policy decision to treat all pediatric patients with chemotherapy after clinical staging. The present study reports the results of treatment with primary chemotherapy.

Subjects and Methods

All children up to 14 years of age are seen in the Pediatric Oncology Department after registration. Between January 1984 and December 1988, 29 children with histologically proven HD were seen in this Department for further evaluation and management. Staging was done only clinically. The pretreatment studies included **a** detailed patient history, and physical examination. Routine laboratory studies including a complete blood cell count with differential count, erythrocyte sedimentation rate, renal and liver function studies were obtained for all children before therapy. All patients had chest roentgenograms, ultrasonography of

abdomen and bone marrow aspiration/ biopsy. Computed tomographic scan of abdomen was done only in 6 cases. Lymphangiogram and staging laparotomy were not done in these subjects. Patients were histologically classified according to the Ryes modification of Lukes and Butler scheme. Clinical staging was determined according to the Ann-Arbor Classification.

Combination chemotherapy with COPP (Cyclophosphamide, Vincristine, Procarbazine and Prednisolone) or MOPP (Nitrogen mustard, Vincristine, Procarbazine and Prednisolone) regimes were given to these patients as the primary modality of treatment; the choice of the regimen was dependent upon the availability of injection Mustine. The dosage used was injection Cyclophosphamide 500 mg/m^2 or injection Mustine 6 mg/m^2 and injection Vincristine 1.4 mg/m^2 intravenously on days 1 and 8. Procarbazine 100 mg/m^2 and Prednisolone 40 mg/m^2 were administered orally from Days 0-14. The cycle was repeated once in 28 days. One Stage I patient received only 4 courses, 5 patients in Stage III received 8 courses and 15 patients received 6 courses of chemotherapy. Three patients with initial bulky disease (lymph node mass > 10 cm diameter) received involved field irradiation at the end of 6 courses of chemotherapy (2000-2500 cGy).

Results

The characteristics of 29 patients are summarized in *Tables I & II.* The age distribution in these 29 patients shows an early peak. The youngest age recorded was 3 years with a median age at diagnosis of 6.5 years. The male: female ratio was 4.8:1. Twenty one patients (72%) presented in the early clinical stages (I and II) with systemic symptoms in 8 (38%). Only 8 patients had clinically advanced disease and systemic symptoms were present in 4 of these. The mediastinal mass exceeded one third of the maximum intra thoracic diameter in one subject. Two patients were upstaged after doing ultrasonography of abdomen. Mixed cellularity (MC) was the most common histopathologic subtype (55.2%) followed by nodular sclerosis (24.1%) and lymphocyte predominant type (20.7%). There was no case of lymphocyte depletion in this series. Seven cases had prior lymph node biopsies and 12 children received anti-tuberculous drugs for lymphadenopathy before the definitive diagnosis of HD was made.

TABLE 1-*Characteristics of Study Population (n=29).*

Feature	Patients No.	(%)
Sex		
Male	24	82.7
Female	5	17.3
Age (yrs)		
< 5	5	17.2
5-9	11	37.9
10-14	13	44.8
Histology		
Mixed cellularity	16	55.2
Nodular sclerosis	7	24.1
Lymphocyte predominant	6	20.7

TABLE II-*Clinical Staging in 29 Patients*

Stage	No.	*Symptoms* No. of patients A	B
I	8 (27.5)	6	2
II	13 (44.8)	7	6
III	6 (20.6)	3	3
IV	2 (6.8)	1	1

Twenty one cases were evaluable for treatment results. Sixteen patients received COPP regimen and 5 patients received MOPP regimen. Complete remission was obtained in 19 children with 2-4 courses of chemotherapy. One patient with Stage IIIB disease at presentation died of progressive disease and sepsis in the 2nd month itself. One patient did not achieve complete remission even after the 4 course of chemotherapy and was given IF XRT. Two children with Stage II disease relapsed in the initial bulky site 12 months and 30 months after stopping treatment. One of the patients was salvaged with chemotherapy (COPP) and is in 2nd remission for 60 months. Other patient refused further chemotherapy and was given mantle irradiation.

He is also alive and free of disease for the last 40 months. One patient with Stage IIIA had persistent enlarged spleen even after completing 8 courses of COPP. A laparotomy and splenectomy was done in this case and histopathological examination of spleen revealed evidence of extramedullary hemopoiesis only. The patient died of respiratory infection 3 months after splenectomy. Sixteen children are in continuous complete remission for periods ranging from 50 to 100 mo, (median survival is 67 mo). The relapse free survival and overall survival were 76% and 86% at 5 years respectively by Kaplan Meier Method *(Fig. 1).*

Myelosuppression requiring dose modification or delay in treatment occurred in all the 5 cases who received MOPP chemotherapy and in one patient who received COPP. Three patients developed hemorrhagic cystitis and injection Endoxan was replaced by leukeran after 3 courses in one patient due to cystitis. One patient developed hepatitis B infection after completing chemotherapy and another patient developed *Herpes zoster.*

Discussion

HD is relatively uncommon and it forms about 2% of all our childhood malignancies. Over the last 3 decades significant changes have occurred in the management in HD in children. Success of combination chemotherapy in late stages of HD and delayed side effects of radiation in children directed us to initiate chemotherapy in all the stages of the disease. Moreover, staging laparotomy with its complications and morbidity could be avoided. Combined modality treatment using combination chemotherapy MOPP and extended field or involved field irradiation produced survival rate over 90% and proved superior to radiation therapy alone in clinically staged patients. Gehan *et al.* in their study of Stages I and II HD in children compared the effectiveness of involved field radiotherapy and chemotherapy, extended field radiotherapy and extended field radiotherapy and MOPP(2). Patients who received chemotherapy and involved field radiotherapy had 95% relapse free survival at 5 years compared to 67% in patients who received extended field irradiation alone. However, the overall survival remained same because of effective salvage chemotherapy. The late effects were more in patients who received both modalities.

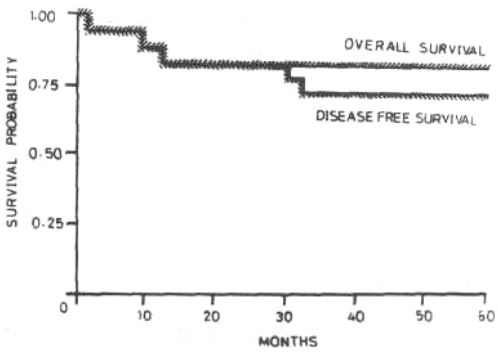

Fig. 1. Survival and disease free sruvival of 21 Hodgkin's disease patients with primary chemotherapy.

Evaluation of the efficacy of low dose radiation along with chemotherapy suggested that 20 gy was adequate dose to cure HD after good response to chemotherapy(3,4). The major advantage of chemotherapy over radiation in children is the absence of impairment of musculoskeletal growth. MOPP chemotherapy has produced 52 to 92% 5 year relapse free survival in children with HD. Experience with MOPP from Uganda and South Africa showed relapse free survival between 75% to 90% for Stages I and II and 40% to 50% for Stages III and IV(5,6). Madanat used MOPP alone in 28 clinically staged children with HD and the relapse free survival and overall survival were 95% and 100%, respectively(7). Lange *et al.* using COPP regimen could produce an overall survival and relapse free survival of 100% and 86% for early stages (I and IIA) and 86% and 60% for Stages IIB-IVB(8). In our series, the overall survival and relapse free survival were 86% and 76%, respectively which are comparable to above reports. The sample size precludes a stage wise survival analysis.

Our results show that staging laparotomy can be avoided in children when chemotherapy is planned. Chemotherapy also has got problems. Alkylating agents like mustine and cyclophosphamide are well known to produce sterility(9). Leukemogenic potential is also high especially where it is combined with XRT. We have not specifically evaluated the late complications; however, no clinical abnormalities were encountered.

In conclusion, combination chemotherapy (COPP/MOPP) has a high cure rate and overall survival irrespective of clinical stage, histological type and presence or absence of 'B' symptoms. It avoids the need for extensive staging evaluation including staging laparotomy and the late growth problems associated with radiotherapy.

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NOTES AND NEWS

"THE CHILD"

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WORLD BREAST FEEDING WEEK

The Indian Academy of Pediatrics, West Bengal Branch, is celebrating this event on 3rd August, 1996 at the Auditorium of N.R.S. Medical College, Calcutta. There will be a Seminar on Human Lactation Management and Baby Friendly Hospital Initiative followed by lectures from different quarters of the community namely Film Director, Artist, Author, Painter, Social Service Organizations, Nurse and A Poster Exhibition.

PALS COURSE

The Department of Pediatrics, St. John's Medical College Hospital, Bangalore under the auspices of IAP is organizing a Pediatric Advanced Life Support (PALS) Course on 17th and 18th August 1996. Registration is restricted to first 40 delegates. The course fee will be Rs. 600/- and should be sent by cheque/DD in the name of **Pediatrics CME.** The programme Coordinators are Dr. Swarna Rekha and Dr. Jairam Sastry. For further details please contact: Dr. Jairam Sastry, Assistant Professor of Pediatrics, St. John's Medical College Hospital, Bangalore 560 034.