**ORIGINAL ARTICLE-I**

# A Pilot Study of BEACOPP Chemotherapy with or without Involved field Radiotherapy in Hodgkin's Lymphoma

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## ABSTRACT

**Background : Prognosis of patients with Hodgkin's lymphoma (HL) has improved significantly during the past two decades. About 20% of patient with advanced HL fail on ABVD chemotherapy. A number of approaches including more intensive multi drug regimen in randomized studies have shown reduced risk of primary failure and a better event-free survival.**

**Patients & Methods : Between April 2000 to Jan.2003, twenty previously untreated, patients with HL were enrolled. Eligibility criteria were- ECOG PS I to III, adequate hematological, renal & hepatic functions. Patients were classified as early stage group ≥=3 Lymph node areas, high ESR (30mm with 'B' symptoms or 50mm without 'B' symptoms, extra nodal involvement or bulky mediastinal mass) or advance stage" group (stage III/IV & stage I & II with any risk factor). Patients in early stage group received 4 to 6 cycles of standard BEACOPP regimen (Etoposide 100mg/m2 on days 1,2,3; Adriamycin 25 mg/m2 on day 1,Cyclophosphamide 650 mg/m2 on day 1,Procarbazine 100mg/m2 days 1 to 7, Prednisolone 40mg/m2 days 1 to 14; Bleomycin 10mg/m2 on day 8 & Vincristine 1.4 mg/m2 (max. 2mg) on day 8. Those with advance stage group, received 6 cycles of modified escalated BEACOPP (Etoposide 100mg/m2 on days 1,2,3, Adriamycin 30mg/m2 on day 1, Cyclophosphamide 650 mg/m2 on day 1, Procarbazine 100mg/m2 days 1 to 7; Prednisolone 40mg/m2 day 1 to 14; Bleomycin 10mg/m2 on days 1 & 8 & Vincristin 1.4mg/m2 (max. 2mg) on days 8. Following chemotherapy, patients received involved field radiation (3000 cGys in early stage group or 4000 cGys in advance stage group with bulky or residual disease.**

**Results: There were 5 patients in the early stage and 15 in the advance stage group. Mixed cellularity histology was most common. A total of 105 chemotherapy cycles were delivered, no patient died of chemotherapy related complications. Grade III/IV anemia, neutropenia, thrombocytopenia were seen in 9.4%, 9.4%, and 5.7% of cycles, respectively. 9.4% of patients needed admission for management of febrile neutropenia.**

**CONCLUSION :**

**Present pilot study confirms the high response rates achieved with dose intensive BEACOPP regimen in our patients population. Toxicity is acceptable.**


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## INTRODUCTION

Outcome of patients with Hodgkin's lymphoma (HL) has improved significantly during the past two decades. Currently, following ABVD (adriamycin, bleomycin, vinblastine and DTIC) and /or radiotherapy complete remission rates for advanced HL exceed 85% to 90% with 5 year over all survival rate of 80%.[1] Outcome in early

stage HL is above 90%. Therefore, present emphasis is to reduce the toxicity of treatment in early stage HL while maintaining the improved outcome. In spite of good improvement , almost 10-20% of patients with advanced HL fail to respond to primary chemotherapy or relapse early.

To improve remission rate and reduce the risk of relapse in advanced HL many investigators have suggested use of multidrug intensive chemotherapy e.g. BEACOPP (bleomycin, adriamycin, etoposide, cyclophosphamide, vincristine, prednisolone and procarbazine) in place of ABVD We have recently conducted a pilot study using this regimen. This report describes the results.

## PATIENTS AND METHODS

Between April 2000 to Jan 2003, twenty three patients were enrolled in this study. Two patients after recruitment were detected to have lymphoma subtype other than HL and were excluded . One patient refused for treatment after first cycle, thus 20 patients were eligible for response to chemotherapy and outcome. At diagnosis- all patients underwent detailed clinical examination, hemogram, liver and renal function tests, chest x-ray, CT scan of chest and abdomen and bone marrow biopsy. Bone marrow biopsy was done in all patients (except early stage group). The modified Cotswold classification was used for staging. Semen analysis & sperm cryopreservation (whenever feasible) was done at base line. Response assessment was done after two cycles & then at the end of treatment. Toxicity assessment (CTC version 2) was done with every cycle. After completion of treatment patients were followed up in outpatients clinic every 3 months in first two years & 6 monthly between 3 to 5 years & then annually. Complete blood counts, ESR, LDH, ultrasound was done every three month & chest x-ray was done every 6 months for first two years & then annually. Semen analysis was re-performed after completion of planned treatment. Confirmation by biopsy was necessary to document relapse/recurrence. Prognostic factors-ESR, 'B' symptoms, stage, number of extra lymphatic areas, bulky disease etc. were recorded (Table - 1).

**Table -1 BEACOPP Chemotherapy Schedule**

| Drug | BEACOPP basic | | | BEACOPP escalated | | | BEACOPP modified escalated | | |
|---|---|---|---|---|---|---|---|---|---|
| | Dose | Route | Day | Dose | Route | Day | Dose | Route | Day |
| Cylophosphamide | 650 mg/m2 | i.v. | 1 | 1250 mg/ m2 | i.v. | 1 | 650 mg/m2 | i.v. | 1 |
| Doxorubicin | 25 mg/m2 | i.v. | 1 | 35 mg/ m2 | i.v. | 1 | 30 mg/m2 | i.v. | 1 |
| Etoposide | 100 mg/m2 | i.v. | 1-3 | 200 mg/ m2 | i.v. | 1-3 | 100 mg/m2 | i.v. | 1-3 |
| Procarbazine | 100 mg/m2 | p.o. | 1-7 | 100 mg/ m2 | p.o. | 1-7 | 100 mg/m2 | p.o. | 1-7 |
| Prednisone | 40 mg/m2 | p.o. | 1-14 | 40 mg/ m2 | p.o. | 1-14 | 40 mg/m2 | p.o. | 1-14 |
| Vincristine | 1.4 mg/ m2 (max.2mg) | i.v. | 8 | 1.4 mg/ m2 m2) | i.v. | 8 | 1.4 mg/ m2 | i.v. | 8 |
| Bleomycin | 10 mg/m2 | i.v. | 8 | 10 mg/ m2 | i.v. | 8 | 10 mg/m2 | i.v. | 1-8 |

Patients were divided in two groups for treatment purpose according to German Hodgkin's Lymphoma (GHL) Study Group. Patients of stage I & II without risk factors were grouped as '*early stage group'* & stage I & II with any risk factor & stage III & IV were grouped as '*advance stage group'*.

**Table-2 : Patients Characteristics**

| Characteristics | No. of Patients (n=20) |
|---|---|
| Age range (years) | 5-62 |
| Median age (years) | 22 |
| Male/female | 14:6 |
| Histology | |
| NLP | 2 |
| Classical | |
| L.P. | 1 |
| N.S | 2 |
| M.C | 14 |
| L.D | 1 |
| Stage(I/II/III/IV) | 2/12/3/3 |
| Risk Group | |
| Early | 5 |
| Advance | 15 |
| Response to Chemotherapy | |
| CR | 17/20 (early 5/5, advanced 12/15) |
| PR | 2/5 (advanced) |
| PD | 1/15 (advanced) |
| Survival at 3 years | |
| Overall | 95% |
| Progression- free | 90% |

NLP- nodular lymphocytic predominant, NS-nodular sclerosis, MC-mixed cellularity, LD-lymphocytic depletion.

## TREATMENT

We adopted basic regimen of BEACOPP from GHL study trial and modified the escalated BEACOPP to eliminate the use of prophylactic G-CSF support. Comparative chart of three types of BEACOPP is given in Table no. 1

Cycles were repeated every 3 weeks. Early stage group received 4-6 cycle of chemotherapy & advance stage group received 6 cycles. Involved field radiation (IFRT) 30 Gys was planned to all early stage group patients & 40 Gys to advance stage group patients with bulky disease, residual disease (Post Chemotherapy) or original site with slow response. Non-responders/minimal-responders after 3 cycles of chemotherapy were put off further chemotherapy & treated separately.

## RESULTS

The median age was 22 years (range' 5 to 62 years) with 14 males and 6 females. Predominant histopathology subtype was mixed cellularity 14/20(70%); majority of patients were stage II disease 12/20(60%) but after risk stratification early stage group patients were 5 & 15 had advance stage group. Median duration of chemotherapy in basic BEACOPP group was 20

weeks (planned 18 weeks) & in modified escalated group 21 weeks (planned 18 weeks). 16/20 (80%) patients completed planned treatment. Among 5 patients with early stage group, 4 received IFRT, one refused for radiation. One patient was lost to follow up after 4 cycles and in 2 patients, modified escalated BEACOPP was changed to basic BEACOPP due to grade III/IV neutropenia. & cost of growth factors. No treatment related death occured.

chemotherapy cycles and two patients were given growth factor support to complete planned chemotherapy schedule.

2 patients had deranged liver function tests and & 3 patients had grade III/IV asthenia (Table - 3)

Follow up : One patient in 'advance stage group' stopped treatment after 4 cycles of chemotherapy. He had very good partial response and is alive at 2 years with progressive disease. Another patient in advance stage group relapsed & expired after 6 months. Third patient developed secondary leukemia after 2 years of treatment and expired. The probability of overall survival and disease free survival for whole group is 95% and 90%, respectively. Two eligible female patients got married and have delivered normal children. Similarly, one male patient got married after treatment and has fathered a normal child.. One female patient at the time of starting BEACOPP chemotherapy was in her 7$^{th}$ month of pregnancy & she delivered a healthy female child.

**Table-3 : Toxicity to Chemotherapy (No of cycles=105)**

| TOXICITY | Grade | |
|---|---|---|
| | I/II (%) | III/IV(%) |
| Anemia | 19 | 9.5 |
| Leucopenia | 9.5 | 4.8 |
| Thrombocytopenia | 5.7 | 2.9 |
| Nausea/Vomiting | 14.2 | 4.8 |
| Diarrhoea | 9.5 | 2.0 |
| Hepatic | 4.8 | 2.0 |
| Documented infection | 3.8 | 2.0 |
| Asthenia/Myalgia | 2.0 | 4.8 |

**Response :** In early stage group, all 5 patients achieved complete response (CR). In advance stage group- 12 (79%) achieved complete (CR), 2 partial (PR) and one had refractory disease. Following involved field radiation (IFRT), one of partial responder achieved CR.

**Toxicity :** A total of 105 cycles of chemotherapy were delivered. Relative dose intensity of chemotherapy was 92% & 86%, respectively compared to basic and modified escalated BEACOPP. Grade III/IV anemia, leucopenia and thrombocytopenia occured in 9.5%, 4.7% and 2.8% of chemotherapy cycles, respectively. Febrile neutropenia was seen in 6% of cycles. Delay in treatment occured in 9.5% of

## DISCUSSION

The outcome for advanced Hodgkin's lymphoma has improved significantly during the past two decades. Cure rates of more than 70% are now possible. ABVD is still considered the gold standard on the basis of the results of a series of randomized controlled trial & a relatively favorable toxicity profile. However 20% to 40% patients progress or relapse & respond poorly to salvage treatment.[9,11] There are two main approaches to improve outcome in advance HL. The first is an increase in dose intensity by changing drug schedule in such a way so as to offer continuous exposure to active drugs on a weekly schedule (eg.Stanford V regimen).The second approach involves escalating the total dose of multiple drug with its inherent risk of toxicity (eg. escalated BEACOPP). Our study is a balance approach to reduce the toxicity & to increase the efficacy by increasing modestly the dose of doxorubicin & bleomycin with the chance of further improvement in the cure rate in high risk cases & reduction in the cost. The rationale for only increasing the dose of doxorubicin & bleomycin is that these two drugs do not have risk of causing sterility and only weak association of doxorubicin in causation of secondary leukemia & bleomycin does not cause myelosuppression. Similarly dose of cyclophosphamide & etoposide is not increased to reduce myelosuppression & reduce possibility of secondary leukemia. However, we observed one case of secondary AML in our study after 2 years denoting possible relation with etoposide. The regimen seems favorable from fertility point of view. Three female patients had amenorrhoea during and after completion of treatment of which two resumed normal menstrual in immediate follow up period & gave birth to normal children. The rationale for the use of radiation for stage III/IV disease is based on the observation of relapse in previously involved bulky sites. 10 of 15 patients in the present study received involved field radiation to bulky sites in the advance stage group. Response rates achieved in the present study in both groups is similar to those reported in larger no of patients. With this regimen it was possible to reduce the duration of treatment from 24 wks of ABVD or COPP/ABVD to 18 wks. While cost of chemotherapeutic drugs in ABVD is Rs. 48000 & basic BEACOPP is Rs. 24000 & escalated BEACOPP with prophylactic G-CSF will be more than Rs. 1,00,000 with six cycle. For modified escalated BEACOPP cost is Rs. 30,000. This is of paramount importance in Indian context, because of increased time duration, cost, & side effects, compliance to treatment is reduced. Thus present pilot study suggests that basic & modified escalated BEACOPP are similar in short term results with mild to moderate side effects. There is need to confirm these observations in Indian setting in a phase III study comparing with current gold standard 'ABVD' regimen.

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