Original Paper

TREATMENT OUTCOME WITH A SECOND GENERATION COMBINATION CHEMOTHERAPEUTIC REGIMEN m-BACOD AND WITH A STANDARD REGIMEN CHOP FOR ADVANCED DIFFUSE NON-HODGKIN'S LYMPHOMA IN ELDERLY PATIENTS

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Abstract

Seventy newly diagnosed elderly patients with non-Hodgkin's lymphoma with diffuse large cell lymphoma patients in stage II to stage IV were treated with two different chemotherapeutic regimens to compare the outcome of treatment. Forty patients were treated with CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisolone) in the standard doses with twenty one days interval for eight such cycles. Remaining thirty patients were treated with m-BACOD (bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone; methotrexate with folinic acid rescue) in standard doses with twenty one days interval for eight such cycles. Patients of CHOP treated group showed better response than that of m-BACOD treated group. The patients treated with CHOP (n=40) showed the complete response in 20 (50%), partial response in 7 (17.5 %), stable disease in 4 (10 %), progressive disease in 4 (10%), death during treatment 5 (12.5 %), death within three years after completion of treatment 18 (45 %) patients and overall survival after three years of treatment was 17(42.5%) . On the other hand patients treated with m-BACOD (n=30) showed the complete response in 14 (46.7%), partial response in 5 (16.7%), stable disease in 2 (6.7%), progressive disease in 3 (10%), death during treatment in 6 (20%), death within three years after completion of treatment in 17(56.6%) patients and overall survival after two years of treatment was 7 (23.3%) . Complete response and overall survival after three years of treatment was higher in the patients treated with CHOP group than the m-BACOD group. The study also showed the toxicities of m-BACOD was much more than CHOP regimen.

Introduction

The non-Hodgkin's lymphoma are a heterogenous group of diseases linked only by their origin within the lymphoid subtypes. The incidence of non-Hodgkin's lymphoma has dramatically increased since 1950s, in both the UK and the USA[1]. Approximately 5000 new cases of non-Hodgkin's lymphoma are registered in England and Wales every year and increasing by 3-5 % per year and they continue to attain more prominence in cancer mortality statistics[2] . The reason for the increasing incidence is not known; better diagnosis, an increasing elderly population and unknown environmental factors may be relevant.

The most frequent type of non-Hodgkin's lymphoma, diffuse large-B cell lymphoma, accounts for approximately 40 percent of new cases of lymphoma[3]. More than half of the patients with diffuse large cell lymphoma are over 60 years of age[4-6] and the treatment of these elderly patients is a difficult challenge. Diffuse large cell lymphoma is characterized by aggressive clinical behaviour, typically presenting with rapidly enlarging lymphadenopathy. All patients to be treated in curative intent. The CHOP regimen (cyclophosphamide, doxorubicin, vincristine and prednisolone) is the standard care for younger and elderly patients with diffuse large cell lymphoma[7], but it induces complete response in only 40 to 50 percent of elderly patients, with three year event-free and overall survival rates of 30 percent and 35 to 40 percent[8] respectively .

Several chemotherapeutic regimen have been introduced such as MACOP- B, m-BACOD , Pro-MACECytaBOM and others but none of these proved to be superior to CHOP. This study showed the outcome of CHOP and m-BACOD chemotherapeutic regimen in the management of stage II to stage 1V diffuse large cell lymphoma .

Materials and Methods

The study was carried out over a period of six years from January 1999 to December 2004, at different hospitals and private clinics, where the patients reported to Haematologist for management. Total 314 cases of non-Hodgkin's lymphoma reported for management at different hospitals and clinics. Seventy patients with diffuse large cell lymphoma age between 50 to 80 (SD±Mean, 64.67±9.98) years irrespective of their sex, race, occupation and body configuration with reasonable economic background capable to support the chemotherapy and related additional supportive measures were included in this study.

The non-Hodgkin's lymphoma was diagnosed by clinical

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findings, peripheral blood examination, bone marrow examination and histological diagnosis by biopsy of lymph node and / or extranodal sites. Biopsy of lymph node and histopathological diagnosis were done by standard procedure. Diagnosis was done according to the histopathological examination report. Revised European - American Lymphoma classification[8] could not be followed due to limitation of investigation facility. Patients were required to have stage II, III or IV disease and a performance status of 0 to 3 according to the criteria of the Eastern Clinical Oncology Group[10]. Patients were excluded from the study, who were with central nervous system involvement, active cancer, unresolved hepatitis B virus infection or any serious active concomitant disease, cardiac contraindication to doxorubicin therapy or a neurologic contraindication to vincristine. All patients gave written informed consent. All the seventy patients were initially hospitalized for management at different hospitals . After confirmation of diagnosis of lymphoma complete clinical work up was carried out by complete physical examination, performance status[10], B symptoms, complete blood count including platelet count, serum LDH, kidney function tests, liver function tests, serum calcium & uric acid level. Also bone marrow examination, X-ray chest, CT scan of chest and abdomen were done. In selected cases HIV test, B_2 microglobulin, lumber puncture and MRI were done. Age and sex of the study sample were documented. Initial clinical findings at the time of diagnosis and subsequent findings during study period were also noted and later analysed to determine the response of treatment.

Table-I : Table showing criteria of selection of patients

Parameters	Criteria for inclusion
Confirmed diagnosis	Confirmed diagnosis of diffuse large cell non-Hodgkin's lymphoma by lymph node biopsy.
Age group	Age range from 50 -80 years
Performance Status	ECOG[10] : 0 - 3
Haematopoietic parameter	Absolute neutrophil count > 2000 / cmm of blood. Platelet count >50,000/cmm . No bleeding or coagulation disorder.
Hepatic parameter	Serum bilirubin not greater than 1.5 times of upper limit of normal (ULN) Serum AST not greater than 2.5 times ULN PT & APTT not greater than 1.5 times ULN. No history of chronic hepatitis or cirrhosis.
Renal parameter	Creatinine not greater than 2 mg/dl
Cardiovascular parameter	No active symptoms of coronary artery disease, congestive heart failure (CHF)
Others parameter	Human immunodeficiency virus (HIV, 1, 2) negative. No other chronic active disease

Individual patients performance status was determined according to the criteria of the Eastern Co-operative Oncology Group (ECOG) [10] as shown below:

Performance status

0 = Normal
1 = Ambulant with symptoms.
2 = Bed rest < 50% of the days.
3 = Bed rest > 50% of the days.
4 = Bed rest whole days.

Patient selection criteria

Criteria considered for selection of non-Hodgkin's lymphoma cases in the study are shown in table 1.

Course of chemotherapy was completed and followed up as explained under the following heading:

Chemotherapy

Two protocols of chemotherapy were selected to compare the response among the two groups of previously untreated patients. In this study choice of treatment was decided random but the condition of the patients and patients desire were also considered while planning the protocol of chemotherapy .

All the seventy patients were treated with chemotherapeutic agents. Eligible patients were randomly treated with CHOP or m-BACOD, forty patients were treated with CHOP and thirty patients were treated with m-BACOD. Patients treated with CHOP received the combination of cyclophosphamide 750mg/ m^2 body surface area on day 1; doxorubicin 50mg/ m^2 body surface area on day 1; vincristine 1.4 mg/ m^2 body surface area upto a maximum dose of 2 mg on day 1; prednisone 40mg/ m^2 body surface area per day for five days from day 1 to day 5. The patients were treated every three weeks for eight such cycles of CHOP .

Patients treated with m-BACOD received the combination of bleomycin 4mg/ m^2 body surface area on day 1, doxorubicin 45mg/ m^2 body surface area on day 1 ; cyclophosphamide 600mg/ m^2 body surface area on day 1; vincristine 1.4mg/ m^2 body surface area upto a maximum dose of 2 mg on day 1; dexamethasone 6mg/ m^2 body surface area per day for five days ; methotrexate 200mg/ m^2 body surface area on day 8 and day 15 with

folic acid rescue 24 hours after methotrexate every 6 hours for 8 doses. The patients treated every three weeks for eight such cycles of m-BACOD .

Haematological and nonhaematological toxicities during chemotherapy were observed and later analysed. Patients who had severe neutropenia or febrile neutropenia after any cycle of chemotherapy were managed with granulocyte colony stimulating factors. When the severe neutropenia and moderate thrombocytopenia persisted during the next cycle the dose of cyclophosphamide and doxorubicin were decreased by fifty percent . When the neutrophil count was lower than 1.5 $x10^9$/L and platelet count less than $100x10^9$/L before a schedule cycle, the cycle was delayed for up to two weeks.

Thorough history, clinical examination and relevant investigations were carried out in detail to evaluate the course of the disease. All the patients were followed up to minimum three years after the eight cycles of chemotherapy in selected intervals.

Response criteria

The parameters considered to observe the response of treatment of the disease are as follows:

Criterion
Improvement of B symptoms
Improvement of performance status as per ECOG : 0 - 3
Increase in Haemoglobin level
Reduction of serum LDH level
Reduction of size of lymph node and/or regression of organomegaly

Results

During the study period a total 314 patients were found to have different types of non-Hodgkin's lymphoma . Table-II shows the incidence of lymphoma in the different age group out of which maximum number of patients 253 (80.6 %) were found in 50 - 80 years. Male, female ratio was 2.3 : 1 . Out of these 253 patients only 70 patients with diffuse large cell non-Hodgkin's lymphoma who were agreed as per selection criteria were included in the study group.

Table -II: Age & sex wise distribution of patients (n = 314)

Age in years	Male (%)	Female (%)	Total (%)
<30	6 (1.9%)	4(1.3%)	10(3.2%)
31 - 40	12 (3.8%)	7(2.2%)	19(6.1%)
41 - 50	20 (6.4%)	12(3.8%)	32(10.2%)
51 - 60	48 (15.3%)	24(7.6%)	72(22.9%)
61 - 70	101 (32.2%)	28(8.9%)	129 (41.1%)
71 - 80	32 (10.2%)	20(6.4%)	52(16.6%)
Total	219 (69.7%)	95(30.3%)	314

Efficacy

The tumour response were completely assayed after eight cycles of chemotherapy and classified as complete response, partial response, stable disease and progressive disease according to the International Workshop criteria[11]. Complete response was defined as the disappearance of all clinical evidence of active tumour for a minimum four weeks and absence of radiologic or biologic abnormalities observed at diagnosis and the absence of new lesions. Partial response was defined as the regression of all measurable lesions by more than 50 percent the disappearance of nonmeasurable lesions and the absence of new lesions. Stable disease was defined as a regression of any measureable lesion by 50 percent or less or no change for the nonmeasureable lesions but without growth of existing lesions or the appearance of a new lesion. Progressive disease was defined as the appearance of a new lesion, any growth of the initial lesion by more than 25 percent, or growth of any measureable lesion that had regressed during treatment by more than 50 percent from its smaller dimensions. The important laboratory parameters before and after treatment among the responders showed the significant improvement of haemoglobin level, reduction of ESR and lowering of serum LDH levels (Table: V). The patients treated with CHOP (n=40) showed that complete response was achieved in 20 (50%) , partial response in 7 (17.5 %), stable disease in 4 (10 %), progressive disease in 4 (10%), death during treatment 5 (12.5%), death within three years after completion of treatment 18(45%) patients and overall survival after two years of treatment was 17 (42.5 %) (Table - IV). On the other hand patients treated with m-BACOD (n=30) showed that complete response was achieved in 14(46.7%), partial response in 5(16.7 %), stable disease in 2 (6.7 %), progressive disease in 3 (10%), death during treatment in 6 (20 %), death within three years after completion of treatment 17 (56.6 %) patients and overall survival after three years of treatment was 7 (23.3 %) (Table - VI). Complete response and overall survival after three years of treatment was higher in the patients treated with CHOP group than the m-BACOD group. The study also showed the toxicities of m-BACOD was much more than CHOP regimen.

Survival was significantly longer for patients treated with CHOP than those treated with m-BACOD. The percentage of overall survival after three years of management was 42.5% (17) treated with CHOP as compared to 23.3 % (7) patients treated with m-BACOD.

Adverse effects

The Table-III show the haematological toxicities that were observed during chemotherapy. All the patients were anaemic during diagnosis and anaemia was persisted in most of the patients during chemotherapy and few patients required blood transfusion. But to combat

Table- III : Haematological toxicities during chemotherapy (n=70)

Parameters	CHOP (n = 40)	m-BACOD (n=30)
Mild to moderate anaemia	28 (70 %)	24 (80 %)
Neutropenia	15 (37.5%)	18 (60 %)
Thrombocytopenia but not less than 50x 109/L	12 (30%)	15 (50 %)

anaemia during management in the study group was not difficult. After initial correction of anaemia during chemotherapy the presence of anemia was observed in 28(70%) patients treated with CHOP and 24(80%) patients treated with m-BACOD . Neutropenia was the most important features during chemotherapy and in few cases absolute neutrophil count was less than $1.5x10^9$/L and the patients were managed with granulocyte colony stimulating factor in different doses . Total neutrophil count when reduced less than $0.5x10^9$/L, treatment was delayed for two weeks. Neutropenia developed in

Table- IV : Nonhaematological adverse events observed in patients during chemotherapy(n=70)

Events	CHOP (%) (n = 40)	m-BACOD(%) (n=30)
Nausea and vomiting	35 (87.5%)	30 (100%)
Alopecia	35 (87.5%)	30 (100 %)
Mucositis	21 (52.5%)	28 (93.3%)
Neurological toxicity	21 (52.5%)	23 (76.7%)
Infection	20 (50%)	22 (73.3 %)
Constipation	17 (42.5%)	12 (40%)
Lung toxicity	11 (27.5%)	10 (33.3%)
Liver toxicity	11 (27.5%)	14 (46.7%)
Renal toxicity	10 (25 %)	8 (26.7%)
Cardiac toxicity	7 (17.5%)	5 (16.7%)

15(37.5%) patients treated with CHOP and in 18(60%) patients treated with m- BACOD. Thrombocytopenia also

Table - IV: Important laboratory parameters before and after chemotherapy among the responders

	CHOP treated 20 responders		m-BACOD treated 14 responders	
Parameters	Before therapy	After therapy	Before therapy	After therapy
Hb level gm/dl (Mean ± SD)	9.1 ± 2.28	11.95 ± 1.04	9.27 ±1.84	11.25 ± 1.54
ESR in mm in 1st hour (Mean ± SD)	71.2 ± 16.35	50.83 ± 7.76	73.3 ±8.15	51.14 ± 9.24
Serum LDH mg/dl (Mean ± SD)	630.83 ± 49.16	340.16 ± 34.38	646.9± 58.13	420.45±68.10

developed in 12(30%) patients treated with CHOP and in 15 (50%) patients treated with m-BACOD but in no cases the count was below $50x10^9$/L and did not required platelet concentrate transfusion (Table-III).

Haematological toxicities were more marked in the patients with m- BACOD group than the patients with CHOP group.

Nonhaematological toxicities during chemotherapy were also observed. The frequency of toxicity in both groups are shown in table IV. Alopecia was most common observation and were present in 35 (87.5%) of the patients treated with CHOP and 30(100%) of patients treated with m-BACOD. Nausea vomiting with different frequency were present in all the patients of both treated groups . Fever and infection were the most important adverse events in both groups. Nine of the total patients died from infection during chemotherapy. Other nonhaematological adverse events observed were neurologic, liver, cardiac and renal toxicities of different grades. But none of these adverse reactions were that much severe enough to stop the chemotherapy.

Discussion

The non-Hodgkin's lymphoma are a varied group of malignancies with many different clinical presentations, histological subtypes and biological behaviors. The primary site of presentation are lymph node, extranodal site, bone marrow and spleen. The commonest subtype in B-cell lymphoma are diffuse large cell lymphoma, followed by follicular lymphoma, plasma cell neoplasm, extranodal marginal zone lymphoma of the mucosa associated lymphoid tissue (MALT) type and mantle cell lymphoma. The commonest type of lymphoma is diffuse large cell lymphoma and most of the patients are elderly and treatment of these elderly patients is a very difficult challenge. Diffuse large cell lymphoma in all cases of NHL is characterized by aggressive clinical behaviour, typically presenting with rapidly enlarging lymphadenopathy. All patients to be treated in curative intent. The development of curative combination chemotherapy for patients with advanced stages of aggressive non-Hodgkin's lymphoma had been one of the major successes of cancer therapy during past two decades. The first generation regimen, CHOP(cyclophosphamide, doxorubicin, vincristine and prednisolone) is the standard care for younger and elderly patients with diffuse large cell lymphoma[7], but it induces complete response in only 40 to 50 percent of elderly patients, with three year event-free and overall survival rates of 30 percent and 35 to 40 percent[8] respectively. Several chemotherapeutic regimen has been introduced such as MACOP-B, m-BACOD, Pro-MACECytaBOM and others but none of these proved to be superior to CHOP[8].

Here in this study the outcome of CHOP and m-BACOD chemotherapeutic regimen in the management of stage II to stage IV diffuse large cell lymphoma were shown. After completion of eight cycles of chemotherapy 87.5

percent of the patients were alive but only 50 percent of the patients showed complete response to treated with CHOP as compared to 79.3 % of the patients were alive but only 46.7% of the patients showed complete

Table-VI: Treatment outcome in two chemotherapeutic groups

Response status	CHOP (%) (n = 40)	m-BACOD (%) (n=30)
Complete response	20 (50%)	14 (46.7%)
Partial response	7 (17.5 %)	5 (16.7%)
Stable disease	4 (10 %)	2 (6.7 %)
Progressive disease	4 (10%)	3 (10 %)
Death during treatment	5 (12.5%)	6 (20.7%)
Death within three years after completion of treatment	18(45%)	17 (56 .6%)
Overall survival after three years of treatment	17 (42.5%)	7 (23.3 %))

(P > 0.05)

response treated with m-BACOD and the studies of Fisher RJ, et al[7], comparison of standard protocol of CHOP with the three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma showed the similar findings. The findings of Sonneveld P et al[8] comparison of a doxorubicin and mitoxantrone in the treatment of elderly patients with advanced diffuse non-Hodgkin's lymphoma using CHOP versus CNOP (cyclophosphamide, novantron, vincristine and prednisolone) in the chemotherapy also showed that CHOP was better than CNOP . On the other hand within three years after completion of eight cycles of chemotherapy 18(45%) patients died treated with CHOP as compared to 17(56.6%) patients died treated with m-BACOD. The percentage of overall survival after three years of management was 42.5% (18) treated with CHOP as compared to 23.3% (7) patients treated with m-BACOD . In this study it was also evident that event free survival among elderly patients with diffuse large cell lymphoma treated with CHOP was better than second generation m-BACOD which is almost similar to the study of Meyer RM, et al standard CHOP in elderly patients with non-Hodgkin's lymphomas[12]. The study of Tirelli U, et al[13] showed that CHOP is the standard regimen in patients >70 years of age with intermediate grade and high grade non- Hodgkin·s lymphomas. Results of the other similar randomized study of the European Organization for Research and Treatment of Cancer Lymphoma Cooperative Study Group[13], Tilly H. et al, (A randomized comparison of ACVBP and CHOP in the treatment of advanced aggressive non- Hodgkin·s lymphomas)[14] in elderly patients also found that CHOP was superior to ACVBP .

CHOP is effective, less toxic than m-BACOD and other more recently developed chemotherapeutic regimens[12,13]. Toxic reactions observed in this study was found more with m-BACOD than CHOP. In a study comparing a regimen of doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisolone (ACVBP) with CHOP in elderly patients, it was found that ACVBP was associated with longer event free survival because patients who received ACVBP had a lower incidence of relapses[14]. But rate of death due to toxic effect of the therapy was higher with ACVBP than with CHOP particularly in patients over 65 years of age and for that reason treatment with ACVBP was not associated with prolonged survival. But recently developed monoclonal antibody against CD-20 was found to be more effective. The addition of monoclonal antibody rituximab with CHOP chemotherapy given for eight cycles to elderly patients with newly diagnosed difuse large cell lymphoma significantly increases the rate of complete response, decreases the rate of treatment failure and relapse, and improves event free and overall survival as compared to standard CHOP alone[2].

Conclusion

The development of curative combination chemotherapy for patients with advanced stages of aggressive non-Hodgkin's lymphoma has been one of the major successes of cancer therapy during last two decades. The first generation regimen, CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) is the standard care for younger and elderly patients with diffuse large cell lymphoma. In the elderly patients CHOP is better chemotherapy regimen than any other second generation combination chemotherapy schedule. The toxic effects of chemotherapy and infection are the most common cause of mortality. The use of granulocyte colony stimulating factors and adequate supportive care have reduced the chemotherapy induced morbidity and mortality.

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