A Phase II Study of Doxorubicin, Vincristine, Cyclophosphamide, Prednisolone (CHOP) Chemotherapy with Intathecal (IT) Methotrexate and Prophylactic Cranial Irradiation in a Patients with High Grade Non Hodgkin's Lymphoma (NHL)

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Objective: The objective of this phase II study was to evaluate the efficacy and toxicity of (CHOP) chemotherapy with intrathecal methotrexate and prophylactic cranial irradiation in patients with high-grade Non Hodgkin's lymphoma. **Method:** From January 2002 to December 2002 tewenty consecutive patients with histopathologically and immunohistochemically confirmed high grade NHL with Ann Arbor stage III & IV were enrolled. ECOG performance status of 0 or 1 was required. Written informed consent was obtained from all patients. Patients with symptomatic meningeal or brain involvement were excluded from the study. Cyclophosphamide 750 mg /m2, vincristine 1.4 mg / m2 (maximum 2 mg), doxorubicin 50 mg / m2 was given I/V on D1 and prednisolone 100 mg PO was given from D1 – D5. Cycles were repeated after every 21 days. Intrathecal methotrexate was given at a dose of 12 mg once during 3rd week, twice weekly on 5th & 6th week and once during 7th week. A total dose of 1800 cGy was given to whole brain in 10 fractions with a daily tumor dose of 180 cGy using a Cobalt 60. Common Toxicity Criteria was used for evaluation of toxicity and WHO criteria for response evaluation. **Result:** All 20 patients were able to complete the planned therapy. Grade IV neutropenia was observed in 45% (9/20) of patients. Episodes of febrile neutropenia were seen in 20%(4/20). Grade II diarrhea was seen in 25%(05/20). 20%(4/20) had grade II cutaneous toxicity. No immediate radiation related toxicity was seen except grade II nausea and vomiting. Overall response was found in 75%(15/20) of patients, CR in 60%(12/20) and PR in 15%(03/20). 15%(03/20) patients showed stable disease and 10%(02/20) had progressive disease. **Conclusion:** This combined modality treatment of CHOP chemotherapy with intrathecal methotrexate and prophylactic cranial irradiation has been feasible and effective with acceptable toxicity in this group of patients with high-grade Non Hodgkin's lymphoma.

Key words: High grade non-hodgkin lymphoma, cranial radiation, intrathecal

Non-Hodgkin's lymphoma (NHL) accounts for 4 - 5% of new cancer each year and is responsible for 5% of deaths with cancer in the United States. It was estimated for the year 2000, that there will be 54,900 new cases of NHL diagnosed in the United States, and that 26,100 people will die with this diagnosis. No such data exist for Pakistan however it is seen as the 4th common tumor in some of reports in country[1].

Currently "REAL" classification is used to classify NHL and it includes immunoblastic lymphoma, lymphoblastic lymphoma, Diffuse, small non-cleaved cell lymphomas[2]. Lymphoblastic and immunoblastic lymphoma account for 30 - 40% of childhood NHL and share many clinical and biologic features with ALL and are treated as ALL[3]. The survival rates of 85-90% have been achieved with different combination chemotherapies without significant mortality and morbidity as reported by several single institution and co-operative groups[4].

Early preventive CNS therapy is critical in the treatment of advanced stage lymphoblastic lymphoma. IT chemotherapy alone or combined with cranial irradiation has been mainstay of CNS preventive therapy.[5] Patient's with (early stage) had sustained remission with single or multiple dose cyclophosphamide where as majority of patient's with advanced tumor relapsed with systemic and CNS disease. Because of the propensity for CNS metastasis, treatment regimens for Burkitt's lymphoma always involve prophylactic therapy to CNS[6].

CHOP is used as a first line therapy in patients with high-grade Non Hodgkin's lymphoma in Pakistan at most of the centers but the intrathecal chemotherapy and prophylactic irradiation is not being used routinely. High dose chemotherapy with stem cell transplant, which is now a new treatment option of high grade NHL is not being practiced in most of our centers in Pakistan because it is very toxic and difficult to manage, therefore there is a need to improve the treatment of high grade NHL so the existing therapeutic modalities should be integrated and also the benefits of CHOP and CNS prophylactic therapy are not fully explored.

Primary objective:
To study the safety and feasibility of combination of CHOP chemotherapy, intrathecal methotrexate and prophylactic cranial irradiation

Secondary objective:
To determine the effectiveness of this combined modality treatment in preventing CNS relapse in patients with high grade NHL. To document the response rate.

Patient's and method

Study design

Open Label, Non-randomized phase II study at single center. Treatment center, Mayo Hospital KEMC Lahore. No. of patient's 20 consecutive eligible patients.

Place of study Department of Radio therapy Mayo Hospital

Inclusion criteria:

- Patient's must have histologically or IHC stain conmfirmed high grade Non Hodgkin's lymphoma of following varity ,Immunoblastic lymphoma ,Small non cleaved cell (Burkitt's and non Burkitt's)
- Patient's with stage III & IV disease.
- Patient must have ECOG/WHO performance status of <2
- Age 14-70 years
- Patients must have adequate haematologic function as defined by platelets >100,000 mm^3 , Hb > 10.0 g/dl ANC >1,500 /uL.
- Patients must have adequate liver function serum Bilirubin level < 1.5 x the upper normal limit ,SGOT ,SGPT < 2.5 x the upper limit of normal for institution.
- Patients must give written informed consent.

Exclusion criteria

- Patients who have received any prior chemotherapy regimen.
- Patient's with symptomatic brain or meningeal involvement.
- Past or present history of deep venous thrombosis.
- The presence of severe concomitant disease.

Pretreatment evaluation

- Patient's detailed history at base line (night sweats, weight loss, fever, neuralgia, musculoskeletal or GI symptoms)
- Thorough physical examination and assessment of KPS on ECOG/WHO scale
- Laboratory investigations including (haemoglobin, WBC count with differential platelets count, total bilirubin, alkaline phosphatase, SGOT, SGPT,LDH, urea, creatinine.)
- Bone marrow examination both trephine and aspirate (Bilateral).
- X ray chest PA view.
- CT scan chest, abdomen pelvis.
- CSF Examinaton.
- Beta 2 microglbulin (optional)

Staging and prognostification

All the patient's were staged according to Ann Arbor staging (Table, 1). Further, more patients will be divided into good and bad prognosis according to International prognostic index. (Table, 2).

Treatment:

Before each chemotherapy cycle body surface area was calculated according to patient's actual height and weight.

A chemotherapy cycle was defined as a 21 days and is given according to the following doses [7]

C Cyclophosphamide 750 mg / m2 I/V D1
H Doxorubicin HCL 50 mg/m2 I/V D1
O Oncovin 1.4 mg/m2 I/V D1 (max. 2mg)
P Prednisone 100 mg PO D1-5

Inj. Mesna was used as uroprotectant at a dose of 400 mg/m2

IT CHEMOTHERAPY & RADIATION SCHEDULE

Methotrexate IT 12mg on week 3, then twice weekly on week 5& 6 and one dose on week 7.

Cranial radiation was given after second cycle on week 6 in 10 fractions 180 cGy daily to a total dose of 18,00 cGy.[8]

Data analysis methods:

This study is designed to see the feasibility and safety of CHOP chemotherapy when combined with intrathecal methotrexate and prophylactic cranial radiation in patients with high grade non Hodgkin's lymphoma. The toxicity profile of completed therapy and the proportion of patients completing therapy is chosen as an index of feasibility. In case of three or more discontinuation of treatment from first 20 patients, 10 additional patients are to be treated and if more than six patients out of thirty are discontinued from treatment because of toxicity the regimen is to be considered unfeasible. This is considered to be in line with the two-stage design of Bryant and Day.[9]

For the measure of efficacy the complete response rate and partial response rate will be reported with respective confidence intervals. SPSS will be used for the analysis of the relevant clinical data.

Evaluation and follow up:

All the patients were evaluated for toxicity according to NCI criteria and RTOG criteria

Total no. of patient's completing the study

All the patients were followed for 1 year to document relapse.

Response criteria:

WHO response criteria for response evaluation was used and is as follows.

Complete response (CR): Complete disappearance of all measurable and evaluable disease. No disease related symptoms. No evidence of nonevaluable disease for 4 weeks. Partial response (PR): Greater than or equal to a 50% decrease under baseline in the sum of products of perpendicular diameters of all measurable lesions. No progression of evaluable disease. No new lesions. Stable disease (SD): Does not qualify for CR, PR, or Progression.

Results

The characteristics of the patients are listed in (Table 3) median age of the protocol patients was 38 years (range 14 -70). All the patients had aggressive high-grade Non Hodgkin's lymphoma with advanced stage (Ann Arbor III / IV) disease.

The most significant toxicities of the study were hematologic (Table-4) in nature.Grade IV neutropenia was observed in 45% ,out of which 25% of patients developed febrile neutropenia.All febrile neutropenic episodes resolved without long term sequellae after the administration of appropriate broad-spectrum antibiotics in a hospital setting.There was no association between age of patients and the liklihood of developing febrile neutropenia.Twenty percent patients developed grade II thrombocytopenia without any complication.

Regarding non hematologic toxicities. Grade II diarrhea was seen in 25%. Three patients had grade II mucositis.No immediate radiation related toxicity was observed except grade II nausea and vomiting (Table 5).

Overall response was found in 75%, CR in 60% and PR in 15%. Three patients showed stable disease and two patients had progressive disease (Table 6).

Table 1: Ann Arbor System

Stage	Area of involvement
I	One lymph node region
IE	One extra lymphatic organ or site
II	Two or more lymph node region on the same side of diaphragm for stage II Localized involvement of a single extralymphatic organ or site and its regional lymph nodes on the same side of diaphragm. (II E)
III	Lymph node region on both side of diaphragm.
IIIE	One extra lymphatic organ or site (localized) in addition to criteria for stage III.
IIIS	Spleen in addition to criteria for stage III.
IIIS E	Spleen and one extra lymphatic organ or site (localized) in addition to criteria for stage III.
IV	One or more extra lymphatic organ with or without associated Lymph involvement (diffuse or disseminated)

Table 2: International Prognostic Index (IPI)

Parameters	Good prognosis	Bad prognosis
Age	< 60	> 60
LDH	<1 times normal	>1 times normal
ECOG	0-1	2-4
STAGE	I – II	III – IV
No of Extranodal Site	< 1	> 1

Table 3, Patient's Characteristics

Characteristics	Patient's characteristics
Age Range	14 ~ 70 Years
Median age	38 years
Male	13 Patients
Female	07 Patients
Karnofsky's Performance Status	
70 ~ 80	15
80 ~ 100	05
Stage	
III	04
IV	16
Histology	
Diffuse Large Cell	16
Small Non Cleaved Cell	04

Table 4: Chemotherapy Toxicity

Toxicity	Grade	%age
Hematologic Toxicity		
Thrombocytopenia	II	20 (4/20)
Neutropenia	IV	45 (9/20)
Non Hematologic Toxicity		
Mucositis	II	20 (4/20)
Diarrhea	II	25 (5/20)

Table 5: Radiation Toxicity

Toxicity	Grade	%age
Nausea	II	20 (4/20)
Vomiting	II	20 (4/20)

Table 6: Responses

Response	%age
Overall Response (OR)	75 (15/20)
Complete Response (CR)	60 (12/20)
Partial Response (PR)	15 (03/20)
Stable Disease (SD)	15 (03/20)
Progressive Disease (PD)	10 (02/20)

Discussion:

Although a subset of patients with aggressive non-Hodgkin's lymphoma (NHL) are cured with combination chemotherapy, the majority still die of their disease. For this reason, it is important to distinguish between patients with aggressive NHL who can be cured with standard approaches and those who require more experimental therapy[10].

In the last two decades, investigators have attempted to improve the cure rate in aggressive NHL by optimizing the standard induction regimen that was administered to all patients[11]. In most cases, induction regimens were created by adding new agents to four-drug cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) backbone and by increasing the frequency of drug admibnistration[12].The early pilot single-institution studies suggested that the resulting regimens were more effective than standard-dose CHOP.However, when these therapies were compared in randomized cooperative group trials that included more representative patients, CHOP was as effective as the newer regimens[13].

These patients with high grade aggressive NHL may present with CNS involvement or came with CNS relapse after the completion of therapy, so CNS prophylaxis is the essential part of treatment for patients with aggressive poor risk NHL.We have treated twenty patients with aggressive high-grade NHL with CHOP chemotherapy and intrathecal methotrexate and prophylactic cranial radiation. The most significant toxicity was hematology in nature, 45% developed grade IV neutropenia,out of which 20% developed febrile neutropenia and were admitted in hospital for appropriate broad-spectrum antibiotic therapy. These febrile neutropenic episode resolve without any long term seqallae and mortality. Overall response was seen in 75% with CR in 60%. Three patients showed stable

disease and two patients had progressive disease which were put on salvage chemotherapy.

The response rates are comparable with less toxicity with a pilot study that was designed to identify the maximum-tolerated dose (MTD) of cyclophsphamide and doxorubicin in a CHOP induction regimen for poor prognostic high grade NHL patients. Although CR was seen in 75% it showed more episodes of febrile neutropenia i.e. 84% and one treatment related death ,as compared to our study CR in 60% and 45% developed febrile neutropenia and no treatment related death[14].

Recent efforts to improve outcome in high-risk patients with aggressive NHL have included a variety of dose intensive approaches with or without stem-cell support. In such studies, investigators have either increased the initial induction therapy or consolidated initial responses to standard induction regimens with additional high-dose therapy[15]. For example, Gianni et al 90 randomized high-risk patients with aggressive NHL to receive either sequential therapy with high-dose single agent cyclophosphamide, etoposide, methotrexate, and subsequent melphalan / total body irradiation with stem cell rescue or standard-dose methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, and Bleomycin (MACOP-B) chemotherapy. In preliminary analysis, patients treated with high-dose sequential therapy had significant better disease free survival than patients treated with standard regimens[16]. However, the improvement in disease free survival did not translate into a survival benefit for patients treated with high-dose sequential therapy because the regimen was initially associated with an increased number of treatment-related deaths[17].

The POG chemotherapy regimen included three cycles of cyclophosphamide, doxorubicin, oncovin, and prednisone (CHOP) followed by 24 weeks of 6- MP and methotrexate. The POG protocols included IT methotrexate for patients with primary tumor in head and neck region. Chemotherapies result in 65% event free survival. Similar results are seen with cyclophosphamide, oncovin, methotrexate, and prednisone (COMP) chemotherapy but only 40% of advanced stage patients of lymphoblastic lymphoma are cured with standard risk ALL regimens (vincristine, steroids, L asparginase, methotrexate, 6 MP)or COMP therapy[18]. The vincristine, doxorubicine, and prednisone (APO) and LSA2L2 regimens are two other successful protocols for high risk or advanced stage lymphoblastic lymphoma. LSA2L2 include ten drugs and the APO protocol includes intensification with doxorubicin and L - asparginase.

Early preventive CNS therapy is critical in the treatment of advanced stage lymphoblastic lymphoma. IT chemotherapy alone or combined with cranial irradiation has been mainstay of CNS preventive therapy[19]. A relatively high frequency of Burkitt's lymphoma (43%) has been reported in a series from Armed Forces Institute of pathology (AFIP) Rawalpindi[20]

All these treatment regimens are quite toxic and very difficult to manage in our setting,as compared to our study which is less toxic and easy to manage.We are also looking for if this combined modality treatment is effective in preventing the CNS relapse in patients with high-grade advanced stage Non-Hodgkin's lymphoma.

Conclusion:

This combined modality treatment of CHOP chemotherapy with intrathecal methotrexate and prophylactic cranial irradiation has been feasible and effective with acceptable toxicity in this group of patients with high-grade Non Hodgkin's lymphoma

References:

1- Greenlee RT, Murray T, Bolden S, Wingo PA. Cancer statistics, 2000. *CA Cancer J Clin 2000; 50:7*

2- Pittaluga S, Bijenens L, teodorovic . Clinical analysis of 670 cases in two trials of the Europeon Organisation for the Research and Treatment of Cancer Lymphoma Co operative Group subtyped according to the revised Europeon American Classification of Lymphoid Neoplasm: a composition with the working formulation. Blood 1990, 10:4358-67.

3- Vekun FM , Sensel MG, Sun L . Biology and treatment of childhood T- lineage acute lymphoblastic leukemia. Blood 1998; 91: 735.

4- Meadows A , Sporto R , Jenkin R . Smilar efficacy of 6 and 18 months therapy with four drugs (COMP) for localized non Hodgkin's lymphoma: a report from the childrens Cancer study Group.J Clin Oncol 1989;7: 92.

5- Reiter A, Scharppe M, Ludwig WB. Intensive ALL type therapy without local radiotherapy provides 90% event free survival for children with T-cell lymphoblastic lymphoma:a BFM Group report, Blood 2000;95:416.

6- Haddy TB, Adde MA, Magrath IT. CNS involvment in small non-cleaved cell lymphoma: Is CNS disease per Se a poor prognostic sign? J Clin Oncol 1991; 9:1973.

7- Fisher RI, Gaynor ER, Dahlberg S. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. N Engl J Med 1993; 328:1002.

8- Picozzi Jl, Coleman CN. Semin Oncol 1990,17:96-103.

9- Bryant J,Day R.incorporation toxicity consideration in to the design of two-stage phase two clinical trials Biometric 1995; 51:1372-83.

10 -Shipp MA: Prognostic factors in aggressive non-Hodgkin's lymphoma: Who has "high-risk" disease? Blood1994; 83:1165-73.

11 Skarin AT, Canellos GP, Rosenthal DS: improved prognosis of diffuse histiocytic and undifferentiated lymphoma by use of high dose methotrexate alternating with standard agents (M-BACOD). J Clin Oncol 1983;1:91-97.

12 - Lepage E, Gisselbrecht C, Haioun C: Prognostic significance of received relative dose intensity in non-Hodgkin's lymphoma patients: Application to LNH-87 protocol. The GELA.

13 - Gordon LI, Harrington D, Anderson J: Comparison of second-generation combination chemotherapeutic regimen (m-BACOD_ with a standard regimen (CHOP) for advanced

diffuse non-Hodgkin's lymphoma. N Engl J Med 1992; 327:1342-49.

14 - Meyer RM, Quirt IC, Skillings JRI: Escalated as compared with standard doses of doxorubicin in BACOP therapy for patients with non-Hodgkin's lymphoma. N Engl J Med 1993; 329:1770-76.

15 - Gianni AM, Bregni M, Siena S: 5year update of the Milan Cancer Institute randomized trial of high-dose sequential (HDS) vs MACOP-B therapy for diffuse large-cell lymphomas. Proc AM Soc Clin Oncol 1994; 13:373, (abstr 1263).

16 Verdonck LF, Van Putten WLJ, Hagenbeek A: Comparison of CHOP chemotherapy with autologous bone marrow transplantation for slowly responding patients with aggressive non-Hodgkin's lymphoma. N Engl J Med1995; 332:1045-51.

17 - Gherlinzoni F, Martelli M, Mazza Pl: Autologous bone marrow transplantation (ABMT) vs DHAP in aggressive non-Hodgkin's lymphomas (NHL) partially responding to first-line chemotherapy.1994; Blood 84:234a (abstr 922).

18 Anderson JR, Jenkin RD, Wilson JF. Long terms follow up of patients treated with COMP or LSA2L2 therapy for childhood non-Hodgkin's lymphoma: a report of CCG-551from the Children's Cancer Group. J Clin Oncol 1993; 11:1024.

19 Weinstein HJ, Cassady JR, Levery R. Long term results of the APO protocol (vincristine,doxobubicin, prednisone) for the treatment of mediastinal lymphoblastic lymphoma. J Clinc Oncol 1983; 1:537.

20 Ahmed M,Khan AB, Mansoor A. Non –Hodgkin's lymphoma Perspective in Pakistan. Ist Ed, Islamabad, Armed Forces Istitute of Pathology, 1993,pp.26-34.