Thesis submitted to the
TamilNaduDr.M.G.R.MedicalUniversity,
Chennai

For the degree of
Doctorate of Medicine (DM)
In
Clinical Haematology

By:
Dr.AnupamChakrapani, MD
For the year: August 2011

Department of Clinical Haematology
Christian Medical College, Vellore.
Tamil Nadu, India.

Diffuse Large B cell Lymphoma

A Single Centre Study

CERTIFICATE

This is to certify that this thesis titled "Diffuse Large B cell Lymphoma: a single centre study", is a bonafide work of the candidate, Dr. Anupam Chakrapani during the period from August 2009 to August 2011 in partial fulfilment, towards the award of degree of Doctorate of Medicine (higher specialty) in Clinical Haematology for the examinations to be conducted by the Dr.M.G.R Medical University in August 2011.

Dr. Alok Srivastava, MD, FRACP, FRCPA, FRCP
(Thesis Guide)
Professor & Head of the Department,
Department of Clinical Haematology,
Christian Medical College, Vellore.

CHRISTIAN MEDICAL COLLEGE
Department of Haematology
VELLORE - 632 004.

Dr. ALOK SRIVASTAVA, MD, FRACP, FRCPA, FRCP
Professor & Head,
Department of Haematology
Christian Medical College
VELLORE - 632 004, TN., INDIA.

CERTIFICATE

This is to certify that this thesis titled "Diffuse Large B cell Lymphoma:a single centre study", is a bonafide work of the candidate, Dr.AnupamChakrapani during the period from August 2009 to August 2011 in partial fulfilment, towards the award of degree of Doctorate of Medicine (higher specialty) in Clinical Haematology for the examinations to be conducted by the Dr.M.G.R Medical University in August 2011.

Dr. Alok Srivastava, MD, FRACP, FRCPA, FRCP
(Thesis Guide)
Professor & Head of the Department,
Department of Clinical Haematology,
Christian Medical College, Vellore.

ACKNOWLEDGEMENT

(In the name of God, Most Gracious; Most Merciful)

I am heartily thankful to my guide and Professor, Dr.AlokSrivastava, whose encouragement, guidance and support from the initial to the final level made this work possible. I take this opportunity to express my gratitude to my teachers,Dr.Vikram Mathews, Dr Biju George,Dr.AuroViswabandya, Dr Aby Abraham and Dr Rayaz Ahmad for their expert opinions and guidance. I would like to gratefully thankProfessor and Head of Department Pathology Dr.Sheila Nair and my colleague Dr Daborah in providing immunohistochemistry data.Iam indebted to all my colleagues and friends in Clinical Haematology for their constant support and encouragement. My deepest and sincere thanks to my parents, my wife Dr Archana and daughter Aastha, who has been my constant source of support and encouragement during this period.Last but not least Ioffer my regards and blessings to all the patients and their families for their co-operation.

CONTENTS

ABSTRACT

ABSTRACT

Background: Diffuse large B cell lymphoma (DLBCL) is a heterogeneous group of B-cell lymphoma with variation in patient survival. Information regarding clinical presentation, staging, prognostic determinant (biological [GCB, non-GCB] and clinical[IPI]), and response to chemotherapy (CHOP and Rituximab CHOP) in exclusively nodal cases of DLBCL is limited.

Aims and Objectives of the study: To analyse the response to chemotherapy (CHOP and Rituximab CHOP) and to access the prognostic significance of IPI and biological sub-grouping of nodal DLBCL cases in our institution.

Methodology: All patients with nodal DLBCL cases who underwent treatment with minimum six months follow up in the Department of Haematology between January 2006 and April 2010 and whose slides and blocks could be retrieved from Department of Pathology were included in the study.

Results: Of the 106 patients, 71(67%) male and 78(73.6%) patients were <60 years of age. 72(67.9%) presented with B-symptoms, 62(58.5%) had stage III/IV, and 80(75.5%) had high LDH at diagnosis. 22(20.8%) had one or more extra-nodal disease and 21(19.8%) had bulk disease. Out of 106 patients 66(62.2%) were in low IPI risk (0,1,2) and 40(37.7%) were in high IPI risk(3,4,5). Based on immune-histochemistry(Hanset.al) we classified 43(40.5%)patients as GCB DLBCL and 63(59.4%) as non-GCB DLBCL. The clinical characteristics of patients in sub groups were similar.The CR+CRu was 88% in Rituximab vs 70.9%% in non-Rituximab treated patients at the end of six cycles of chemotherapy (p=0.082). After a median follow up of 36 months (range:6-44months in RCHOP and 6-42 months in CHOP),the three year cumulative relapse free survival(RFS) and overall survival(OS) was 56.4% and 74.5% respectively in those who received CHOP chemotherapy. The addition of Rituximab improved the cumulative RFS and OS to 86.3% and 76.5% respectively, though the difference was not significant.

Addition of Rituximab in high IPI risk group patients, improve EFS and OS at 24 months to 74.9% and 83.3% vs 19.8% and 41.5% in CHOP group(p=0.002). Rituximab treated patients in either GCB or non-GCB subgroup had similar EFS and cumulative RFS at median follow up of 24 months in comparison to non-Rituximab patients. In GCB group of patients the Rituximab significantly improves the OS (89.1%vs50.3%) at median follow up of 24 months (p=0.02). Neutropenia with or without fever was the most common chemotherapy related complication and was significantly more in RCHOP patients 68.6% vs 47.3% (p=0.032).

Conclusion: This is the largest series of patients with DLBCL comprehensively evaluated and analyzed for outcome after treatment with CHOP and RCHOP. Patients were classified into low and high IPI risk group as well GCB and non-GCB origin of their disease. Addition of Rituximab has significant advantage in GCB and high IPI risk subgroups. In non-GCB and IPI low risk sub group, Rituximab increases relapse free survival but not the overall survival. Further analysis needs to be done with more number of patients and longer follow-up to truly understand the trend observed in this study for patients in India.

INTRODUCTION

Introduction

Diffuse Large B cell Lymphoma (DLBCL) is a neoplasm of B cells of hematopoietic system. Approximately one-third of all adult lymphomas are DLBCL, the most commonly occurring form of non-Hodgkin lymphoma (NHL) in the western world and India[1,2,3].DLBCL is associated with an aggressive natural history, with median survival of less than one year in untreated patients. The cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP) chemotherapy has been the mainstay of therapy for several decades (six years overall survival 33%), since more intensive chemotherapy were more toxic and failed to demonstrate additional benefits[27,28].

In largely separate efforts, remarkable progress has been made during the past decade in understanding the biological heterogeneity of DLBCL and improving survival for DLBCL patients with combination of CHOP and immunotherapy[29].The integration of anti-lymphoma antibodies, notably rituximab®,into combination therapies for DLBCL have markedly improved patients outcomes across all subtypes[32,33,34]. Microarray analysis, gene expression profiling (GEP) has uncovered distinct molecular signatures for DLBCL subtypes that have distinct clinical behaviours and prognoses[16,17,23]. Various immune-histochemical algorithms have been developed to predict the almost similar results as GEP[21,22]. Most recently, molecular signatures identified through GEP not only contributed prognostic information, but also have aided the new therapeutic targets. There is very minimal data from India on DLBCL looking into the cell of origin based on immunohistochemical algorithm and comparing the response of therapy in different sub-type.

The present study is a retrospective review of response of CHOP and RCHOP chemotherapy in nodal DLBCL cases classified based on immunomarkers into germinal cell (GCB) and non-germinal(non-GCB).

REVIEW OF LITRATURE

Review of literatures

Introduction

DLBCL is a neoplasm of large B lymphoid cells with nuclear size equal to or exceeding normal macrophage nuclei or more than twice the size of a normal lymphocyte that has a diffuse growth pattern. The WHO system modified DLBCL classification to recognize multiple morphologic variants based on improved understanding of the variety of molecular abnormalities associated with DLBCL[8 (Table:1)].

Table:1World Health Organization Classification of Mature Large B-cell Neoplasm

CLASSIFICATION
Diffuse large B-cell lymphoma (DLBCL),NOS
T-cell/histolytic rich large B-cell lymphoma
Primary DLBCL of the CNS
Primary cutaneous DLBCL,leg type
EBV+ DLBCL of elderly
DLBCL associated with chronic inflammation
Lymphomatoidgranulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
ALK+ large B-cell lymphoma
Plasmablastic lymphoma
Large B-cell lymphoma arising in HHV8 associated multicentriccastleman disease
Primary effusion lymphoma
B-cell lymphoma,unclassifiable,with features intermediate between diffuse large B-cell lymphoma and Burkit lymphoma
B-cell lymphoma,unclassifiable ,with features intermediate between diffuse large B-cell lymphoma and classical Hodgkin lymphoma

Epidemiology

Lymphomas are the fifth most common systemic cancer, with the most common subtype being diffuse large B-cell lymphoma followed by follicular lymphoma and Hodgkin lymphoma. DLBCL represents approximately 30% of all lymphomas and is the most common subtype throughout the world[1,4]. In two large epidemiological study the reported incidence in India is 34%[2] and 59.3%[3] respectively. It is more common in the elderly .The median age is in the 7th decade but it may also occur in children and young adults. It is slightly more common in males than in females[1,2,3].The incidence of NHL increased dramatically from the 1970s until the middle of the 1990s with an estimated 65,540 new cases expected in the united states in 2010.Several factors have contributed to this increased incidence including : more sensitive methods for identifying diagnostic cases, improvement in cancers reporting for haematological malignancies, changes in the classification systems used for lymphoid malignancies, and the epidemic of HIV infections occurring during this period with an associated increase in HIV-associated lymphomas[5].For the majority of patients, the aetiology of DLBCL remain unknown. Some factors that influence the risk of lymphoma include genetics, co-morbid diseases or their treatments (notably immunosuppressant), environmental factors such as ultraviolet,pesticide ,hair dyes, and diet. A subset of DLBCL, including immune-blastic and primary central nervous system (CNS) disease, is highly associated with Epstein-Barr virus although, unlike certain indolent histologies, the concept of antigen driven lymphoma genesis is less developed in DLBCL[6].

Clinical Presentation

Most commonly patients present with a rapidly enlarging, painless lymph node in cervical, inguinal or axillary region. However in up to 40% of patients, the initially identified site is extra-nodal commonly involving the skin, gastrointestinal tract, central nervous system (CNS), lung, genitourinary tract or the bones[7]. Approximately 15% of the patients present with bone marrow involvement, about one-third have B-symptom (fever, night sweat, and weight loss),nearly one-half have Ann-Arbor system stage III/IV disease, and more than one half have an elevated serum lactate dehydrogenase (LDH)level[5].

Clinical Prognostic Factors

Originally proposed in 1993,the international prognostic index(IPI) remains the primary clinical tool used to predict outcome for patients with DLBCL[9].StageIII/IV disease, elevated LDH, age>60,Eastern Cooperative Oncology group(ECOG) performance status>2, and involvement of >1 extra-nodal site form the IPI score, with one point to each factor. The IPI scoring system nicely stratified patient into four groups with five years survival of 73%,51%,43% and 26% for 0-1,2,3,4-5 risk factors res with CHOP based regimen[9].However ,the IPI was developed in the era before rituximab was routinely included in treatment regimen. To address this issue.Sehn and colleagues performed a population-based, retrospective, cohort analysis of 365 patients with newly diagnosed DLBCL treated with rituximab plus standard chemotherapy[11]. Although the IPI remained prognostic in this study, it no longer distinguished four outcome groups. With redistribution of the IPI factors into a Revised IPI(R-IPI) grouping.,3 separate categories were defined that provide more accurate prediction of outcome. Patients with zero risk factors had a >90% chance of 4-year

progression free survival(PFS):those with 1-2 risk factors had >80% expected PFS;and those with >3 risk factors had >50% PFS[11].

Currently ,the original IPI remains as a prospectively designed and validated measure for assessing DLBCL risk[12]. In 2007,the revised International Working Group response criteria for malignant lymphoma strongly recommended the use of PET scan for patients with routinely FDG-avid, potentially curable lymphoma such as DLBCL[13,14] .The PET is recommended 1)Before treatment to better delineate the extent of disease[13,14],2) six to eight weeks after completion of therapy for assessment of complete response(CR) because CR is required for cure in DLBCL[13,14],and3) in the context of clinical trial mid treatment to evaluate the prognostic ability of interval PET to predict the ultimate response to therapy and long term outcome[15].

Biological Prognostic Factors

To segregate DLBCL into biological meaningful subgroups that might identify rational therapeutic targets, the Leukemia and Lymphoma Molecular Profiling Project began gene expression analyses of DLBCL biopsy sample by using DNA microarrays and identified biological distinct and prognostically meaningful molecular subgroups of DLBCL[16,17].The first group had a gene expression profile pattern clustered with normal germinal center B cell and was labeled as the GCB variants. The second group had a contrast set of signature genes similar to activated B cells, and thus was termed the ABC variant. The patients in GCB subgroup had a higher 5 year survival rate(60% vs 35%;P<.001)[16,17]. Molecular subtype had shown to predict survival independent of IPI risk[17].Other biological markers including the antiapoptotic protein,Bcl-2, Bcl-6(a marker of germinal center derivation), and Myc(aprotoncogenetranscription factor) carry prognostic significance in DLBCL, and these are now being explored for interacting effects with ABC and GCB subtypes, PET scan

imaging, and modern therapies[18,19,20].Despite its usefulness, gene expression profiling technology has not moved easily into community practices.

As a result, immune-histochemical algorithm have been proposed and validated for classification of DLBCL into GCB and non-GCB(ABC)[21,22]. (Fig:1)

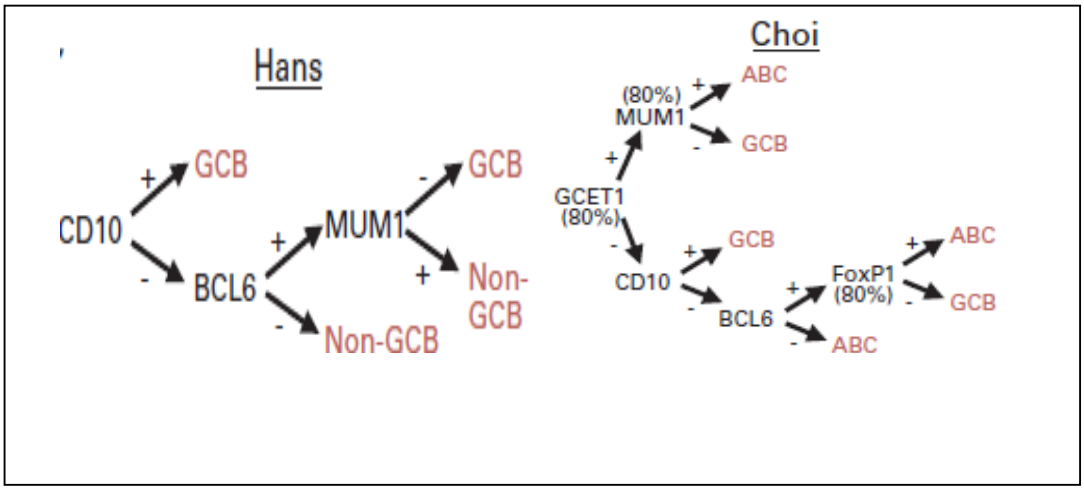


Fig:1 Immunohistochemistry based classification of DLBCL.

An initial algorithm proposed by Hans et al[21] used CD20,CD10,Bcl-6and MUM1(Fig:2) to distinguish GCB and non-GCB subtype(mostly ABC) with 86% concordance with gene expression profiling. More recently ,a consortium of haemato-pathologist improved on Hans method by employing different immunostains, GCET1,CD10,BCL6,MUM1 and FOXP1(Fig:2) and derived a new algorithm with 93% concordance with gene expression profiling[22]. Sub-classification on the basis of cell of origin is predictive of survival in patients with DLBC; who were treated with Rituximab. In the GCB group significantly better overall survival(OS) and event free survival(EFS) than in the non-GCB subgroup(3 years OS 85% vs 69% and 3 years EFS 67%vs 52%)[23,24].Multivariate analysis has showed prognostic impact of the sub-classification on the basis of cell of origin on OS and EFS[23,24].Multivariate analysis of the component of the IPI showed LDH is a significant predictor of both OS and EFS[23].The expression of Bcl-2 and lack of expression of Bcl-6 associated with adverse outcome with CHOP chemotherapy but not with R-CHOP chemotherapy[25,26].

Treatment and outcomes

Newly diagnosed patient

Although DLBCL is associated with a median survival of less than 1 year in untreated patients[1],this disease is commonly curable with conventional anthracycline-based chemotherapy. Advances in the management of DLBCL during the last decade , including the advent of monoclonal antibodies have led to excellent outcomes for many patients. Until recently, the CHOP regimen developed in 1970s[28], remained the standard therapy for DLBCL[27,28]. The Southwest Oncology Group(SWOG) and the Eastern Cooperative Oncology group(ECOG) ,prospective randomized phase 3 trial that compared CHOP to three aggressive multi-agent regimen(m-BACOD,ProMACE/CytaBOM and MACOP-B) ,concluded that the standard CHOP regimen produced similar survival outcome with less toxicity (6 years OS for CHOP regimen was 33% as compared to 36%,34%,and 32% respectively for other three regimens)[27].In 1997 ,rituximab became the first monoclonal antibody approved for the use by US (FDA) for follicular lymphoma, and this immunotherapy was soon applied to DLBCL and other B-cell lymphomas[29,30,31]. Groupe d' Etude des Lymphomes de l'Adulte (GELA) study[32,33,34] in 2002 compared R-CHOP with CHOP alone in patients older than 60 years, showed CR rates were significantly higher in patient who received R-CHOP than the group who received CHOP alone(76% vs 63%; P<.0005),and 2 year OS improved from 57% to 70%(P<.007)[34].Updates of this trail demonstrated that the EFS,PFS and OS remained statistically significant in favors of R-CHOP and actually continued to improve[35]. Results from the GELA trial were confirmed in a US Intergroup trial in older patients[36]. The benefits of rituximab in younger patients was addressed by Mab-Thera International Trial(MInT),in which 824 patients were randomly

assigned 6 cycles of rituximab CHOP or CHOP like chemotherapy or same chemotherapy alone. The three year EFS and OS were 79%vs59% and 93%vs 84% respectively, clearly better in rituximab group[37].On the basis of above observations ,it is clear that rituximab containing regimen improve survival (EFS by 20% and OS by15%) for DLBCL patients regardless of age[38].Among patients who presents with bulky disease, R-CHOP followed by radiation has been considered standard therapy[38].

Relapsed patients

Although the adoption of R-CHOP as the new standard of care has improved outcome for DLBCL, patients still relapse. A multicenter PARMA trail showed that in relapse group of patients two cycles of intensive chemotherapy followed by autologus stem cell transplant(ASCT) improves the EFS and OS(46%vs12% and 53%vs32%) in ASCT group than only chemotherapy group[39,40].A recent evidence based review on the role of ASCT in the management of DLBCL continues to recommend ASCT as the salvage therapy for patients with chemo-sensitive relapsed DLBCL[41].The choice of salvage chemotherapy after R-CHOP failure was addressed by prospective multicenter phase 3 study, the Collaborative Trail in Relapsed Aggressive Lymphoma(CORAL)[43].DLBCL patients were randomized to receive salvage 3 cycles of R-ICE or R-DHAP followed by ASCT in the responders. The overall response rate(63.5%vs62.8%),3-year PFS(31%vs42%)and 3-year Oss(47%vs51.5%)for R-ICE and R-DHAP were not statistically different suggesting that either regimen can be used for salvage therapy[42,43]. Factors that affect 3-year OS include1) second line age adjusted IPI>2 (32%vs62%),2) relapse<12 months after completion of first line therapy (39%vs64%) and3) prior rituximab exposure in frontline setting (40%vs66%)[41,42,43].

Novel Therapies for DLBCL

Although rituximab and R-chemotherapy regimens have greatly improved response rates and survival for patients with DLBCL, relapse[11] remains a consistent clinical problem. Of particular concern are preliminary data from the CORAL trial indicating that although DLBCL is commonly cured with first-line R-CHOP, and many patients have been salvaged at relapse with ASCT in the past,[41,42,43] current DLBCL patients are at higher risk when they relapse early following upfront R-CHOP chemotherapy and have a poor response to second-line rituximab-containing regimens even when theseregimens are consolidated with high-dose therapy and ASCT.[42,43]Novel approaches clearly are needed for DLBCL patients who relapse early after R-CHOP chemotherapy. These include other antibody therapies, lenalidomide[51,52], SGN-40, bevacizumab, Syk inhibitors[45] (fostamatinib disodium), enzastaurin[50], histone deacetylase inhibitors, bortezomib[47], antisurvivin agents, and mTOR inhibitors.[44]A multicenter clinical trial that uses the Hans method to subtype DLBCL patients and then randomizes non- GCB patients to bortezomib plus R-CHOP or RCHOP alone is now underway[46,47,48]. Whereas rituximab was the first monoclonal antibody approved for B-cell NHL and clearly has revolutionized therapy for DLBCL, other antibodies targeting B-cell lymphomas are now available on an investigational basis, including AME-133, GA101, veltuzumab (all CD20), epratuzumab (CD22), dacetuzumab (CD40), galiximab (CD80), lexatumumab (TRAIL), as are other approaches to improve antibody therapy such as conjugation with radioisotopes or toxins[53]. Ultimately, understanding mechanisms by which malignant B-cells become resistant to rituximab and chemotherapy and determining means to address these mechanisms may provide pathways for approval of novel agents. Moreover, defining the biology of resistance and activity for various agents across DLBCL subtypes will

become increasingly important in the future as we attempt to select among regimens for newly diagnosed and relapsed patients.

AIMS & OBJECTIVES

AIMS AND OBJECTIVES

1. To sub classify the Diffuse large B cell lymphoma (DLBCL) in two group Germinal center(GCB) and non Germinal center(non-GCB) on the basis of expression of the three immunomarkersCD10, multiple myeloma oncogene 1 (MUM1), and polyclonal B-cell lymphoma 6 (BCL6)] .
2. To ascertain biological and clinical presentation, staging and international prognostic index (IPI).
3. To assess the response of chemotherapy (CHOP and Rituximab CHOP) in DLBCL as whole and in two subgroup(GC, non GC).

HYPOTHESIS

1. Diffuse large B cell lymphoma sub-classification based on Immuno-histochemical (IHC) stain algorithm on using formalin-fixed, paraffin-embedded tissues will correlates with historical data on gene expression profile.
2. Cell based origin and sub-classification will have prognostic impact on overall survival and event free survival.
3. The prognostic value of the DLBCL subgroup is statistically independent of the features included in the International Prognostic Indicator (IPI).
4. Addition of Rituximab to standard chemotherapy improves the survival of patients with DLBCL, and in both GCB and non GCB group.

PATIENTS AND METHODS

PATIENTS AND METHODS

This study protocol was approved by our Institutional Review Board (IRB).

Duration of the Scheme: January 2006 to April 2010.

Settings of the study: Department of Clinical Haematology, Department of Pathology

Diagnostic criteria:

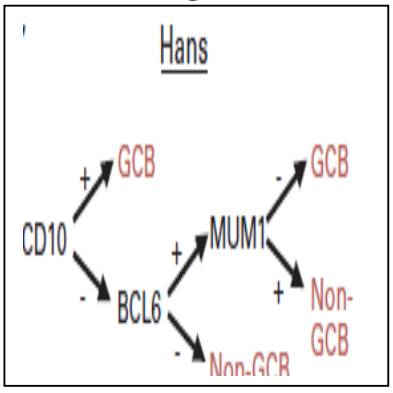
Morphology: The involved tissue should fulfil the morphological description as per WHO 2008(World Health Organization Classification of Mature Large B-cell Neoplasm): Infiltration of the tissue by large B lymphoid cells with nuclear size equal to or exceeding normal macrophage nuclei or more than twice the size of a normal lymphocyte that has a diffuse growth pattern.

Immunomarkers: For Germinal center(GCB), nonGerminal centre(nonGCB) sub-grouping.

Table:2

Markers	Hans classifier*
CD20	POSITIVE
CD3	REACTIVE T-Cells
CD10	>30%
BCL6	>30%
MUM-1	>30%

Fig:2

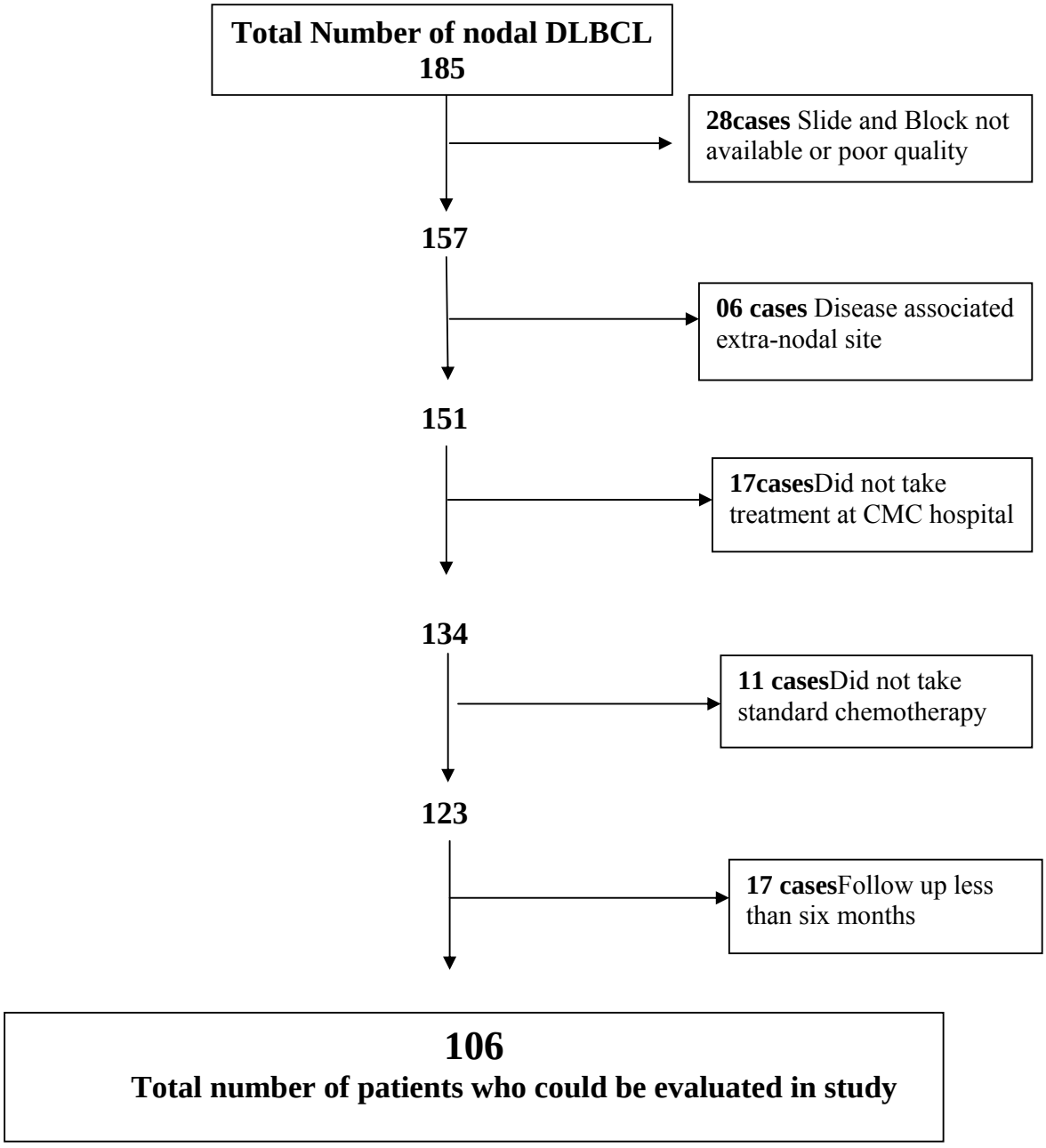


*.Christine P. Hans et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. Blood. 2004;103:275-282

Table:3 Antibody used for Immunohistochemistry

Antibody	Clone	Source	Antigen Retrieval
CD20	L26	DAKO	Citrate(HIER)
CD3	F7.2.38	DAKO	EDTA(HIER)
CD10	56C6	NOVOCASTRA	EDTA(HEIR)
MUM-1	MUMIP	DAKO	EDTA(HIER)
BCL2	124	DAKO	Citrate(HIER)
BCL6	1B6	NOVOCASTRA	EDTA(HIER)

Table:4 Number of DLBCL patients studied



PATIENTS

Inclusion criteria:

1. All the patients of primary nodal DLBCL disease diagnosed at CMCH will be taken as cases.

2. Cases of primary nodal DLBCL who have completed 6 cycles of CHOP/R-CHOP chemotherapy and have a minimum of 6 months follow-up.

3. Availability of hematoxylin and eosin stained and Immunohistochemistry slides from archival.

4.All cases should be CD20 positive.

Exclusion criteria:

1. Transformed DLBCL,

2. Primaryextra-nodal

3. Followup less than six months

4. Paediatric DLBCL cases (age<15 years)

METHODS

Data collection

After approval by the IRB, the patient data base at our institution were reviewed to identify all adults who has been diagnosed as primary nodal DLBCL and received either CHOP or Rituximab CHOP chemotherapy with minimum six months follow-up fromJanuary 2006 to April 2010. Patients who have been diagnosed earlier, their clinical data and histopathology paraffinblock were obtained and rreview of haematoxylin and eosin stained and Immunohistochemistry slides from archival material were done. Paraffin embedded, formalin fixed tissue blocks were used where additional IHC stains was required. The patients were sub-grouped as Germinal center (GCB) and non-germinal center (GCB) as per Hans classifier(Table:2,3).Medical information (regarding the clinical details at diagnosis, during treatment, post treatment status and follow up and other co-morbidities)and blood reports, bone marrow aspirate and biopsy, radiological evaluation were obtained from the patients themselves, or review of their hospital records (laboratory reports/ physician documentation in hospital charts/hospital discharge summaries). Patients were stages as per Ann-Arbor staging system and IPI clinical scoring were done as per Shipp et al data. Patients were treated by either CHOP chemotherapy or Rituximab CHOP chemotherapy.Patients who did not get reviewed or contacted (by telephonic) in the last one year were categorised as '**lost to follow up'.**

Chemotherapy Protocols

RCHOP Chemotherapy:

Inj Rituximab 375mg/m^2 Day 1

Inj Cyclophosphamide 800mg Day 1

Inj Adriamycin50 mg Day1

InjVincristine1.4mg Day 1

Tab Prednisolone 60mg Day 1-5

CHOPChemotherapy:

Inj Cyclophosphamide 800mg Day 1

Inj Adriamycin50 mg Day1

InjVincristine1.4mg Day 1

Tab Prednisolone 60mg Day 1-5

Total six cycles of chemotherapy repeated every 21 days .

Intrathecal Chemotherapy: Inj Methotrexate 12.5 mg with each cycle.

Radiotherapy: As per the indication , dose decision by Deparment of Radiotherapy

Response criteria:

- **Complete response (CR):**Complete resolution of all clinically and radiologically detectable disease, all lymphoma related symptom, and all lymphoma related biochemical abnormalities (like elevated LDH). Lymph nodes and nodal masses must regress to normal size (defined as <1.5cm for lymph node initially >1.5cm). Lymph nodes measuring 1.1 to 1.5cm must regress to <1cm in greatest transverse diameter, or by more than 75% of the sum of the perpendicular diameter (SPD).
- **Complete Response unconfirmed(CRU):**The patient who fulfill criteria for CR with following exceptions, ie;Residual lymph node mass more than 1.5cm in maximum transverse diameter which have regressed more than 75% of the SPD. Individual node which were previously confluent must regress by more than 75% of the SPD compared with the size of the original mass.
- **Partial response (PR):** More than 50% decrease in SPD or no increase in size of the other lymph node, liver or spleen. Spleneic or liver nodule must regress by at least 50% in SPD and or appearance of new lesion.
- **Progressive Disease(PD):** More than or equal to 50% increase from the nadir in the SPD or any previously identified abnormal node 25% in longest diameter or appearance of new Lesion.
- **Stable Disease(SD):**Less than PR but more than a progressive disease.

IPI (International Prognostic Index)

1. Age: more than 60 years
2. Performance status(ECOG): of 2 or higher
3. Serum Lactate Dehydrogenase (LDH): level 1X normal
4. Extra-nodal sites: of 2 or more
5. Stage: III or IV

Staging: The Ann ArborStaging,modifiedCostwald

Stage 1: NHL is limited to one lymph node group (e.g., neck, underarm, groin, etc.) above orbelow the diaphragm, or NHL is in an organ or site other than the lymph nodes (extra-nodal) but has not spread to other organs or lymph nodes.

Stage 2: NHL is limited to two lymph node groups on the same side of the diaphragm, or NHL is limited to one extra-nodal organ and has spread to one or more lymph node groups on the same side of the diaphragm.

Stage 3: NHL is in two lymph node groups, with/without partial involvement of an extranodalorgan or site above and below the diaphragm.

Stage 4: NHL is extensive disease,bone marrow involvement

Additional Designations

A - absent (no) symptoms.

B - Presence of any of the following B symptoms: fever (greater than 101.5°), drenching nightsweats, unexplained weight loss of 10% or more within the last 6 months, severe itching

.

E -involvement of a single extranodal(other than the lymph nodes) site that directly adjoins or is next to the known nodal group.

X - Presence of "bulky" disease, that is, a nodal mass whose greatest dimension is more than 10 centimeters in size, and/ora widening of the mediastinum (middle chest) by more than one-third.

Performance score: ECOG

0. Asymptomatic (Fully active, able to carry on all predisease activities without restriction)
1. Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work)
2. Symptomatic, <50% in bed during the day (Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours)
3. Symptomatic, >50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours)
4. Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair)
5. Death

Data analysis

Statistical analyses were performed with SPSS (windows 11.01 version, SPSS inc, Chicago), for all variables. Descriptive statistics was calculated for all variables. The χ^2 test/ Fishers exact test or *t*-test / Mann Whitney U test was used as appropriate to compare the differences between groups for response to therapy. Overall survival (OS) was defined as the time from initiation of treatment to death or lost follow up. Event free survival (EFS) was defined as the time from initiation of treatment till first event or lost follow up. The event can be loss of response or death. The probability of OS and EFS was estimated using Kaplan-Meier method. For all tests, a two-sided *p*-value of 0.05 or less was considered statistically significant.

RESULTS

Table:5 Patients Characteristics

Patients characteristics	Total Patients N=106(%)	Groups		p
		RCHOP n=51(%)	CHOP n:55(%)	
Age, years				
Median		53	48	
Range	20-79	20-76	21-79	
<60	78(73.6%)	38(74.5%)	40(72.7%)	
>60	28(26.4%)	13(25.5%)	15(27.3%)	1.00
Sex				
Male	71(67%)	35(68.6%)	36(65.5%)	
Female	35(33%)	16(31.4%)	19(34.5%)	0.837
Performance Score(PF)				
=<2	75(70.8%)	36(70.6%)	39(70.9%)	
>2	31(29.2%)	15(29.4%)	16(29.1%)	1.00
Bone marrow involved	23(21.7%)	12(23.5%)	11(20%)	0.814
B-symptom	72(67.9%)	32(62.7%)	40(72.7%)	0.303
Bulk Disease	21(19.8%)	8(15.7%)	13(23.6%)	0.339
Stage				
I/II	44(41.5%)	21(41.2%)	23(41.8%)	
III/IV	62(58.5%)	30(58.5%)	32(58.2%)	1.00
Extra-nodal if any	22(20.8%)	13(25.5%)	9(16.4%)	0.303
LDH				
High(>460 u/dl)	80(75.5%)	37(72.5%)	43(78.5%)	0.652
Normal(<4660 u/dl)	26(24.5%)	14(27.5%)	12(21.8%)	

TABLE:6 Clinical and Biological Characteristics

	Total(n:106)	Groups	
		RCHOP(n:51)	CHOP(n:55)
IPI Score			
Low(0,1)	30(28.3%)	15(29.4%)	15(27.2%)
Low Intermediate(2)	36(33.9%)	17(33.3%)	19(34.5%)
High Intermediate(3)	26(24.5%)	12(23.5%)	14(25.4%)
High(4,5)	14(13.2%)	7(13.7%)	7(12.7%)
Low Risk(0,1,2)	66(62.2%)	32(62.7%)	34(61.8%)
High Risk(3,4,5)	40(37.7%)	19(37.2%)	21(38.1%)
IHC-defined subgroup			
GCB	43(40.5%)	23(45%)	20(36.3%)
Non-GCB	63(59.4%)	28(54.9%)	35(59.4%)

Table:7 Clinical characteristics in GCB and Non GCB subgroup

	GCB n=43 (40.5%)			Non GCB n=63 (59.5%)		
Clinical features	**RCHOP n=23 (53.5%)**	**CHOP n=20(46.5%)**	**p**	**RCHOP n=28 (44.4%)**	**CHOP n=35 (55.6%)**	**p**
Age >60 years	7(30.4%)	5(25%)	0.745	6(21.4%)	10(28.5%)	0.572
<60 years	16(69.6%)	15(75%)		22(78.6%)	25(71.4%)	
Sex Male	17(73.9%)	9(45%)	0.068	18(64.3%)	27(77.1%)	0.279
Female	6(26.1%)	11(55%)		10(35.7%)	8(22.8%)	
Stage I,II	10(43.5%)	8(40%)	1.00	10(35.7%)	11(31.4%)	0.802
III,IV	13(56.5%)	12(60%)		18(64.3%)	24(68.5%)	
B-symptom Yes	15(65.2%)	15(75%)	0.526	17(60.7%)	20(57.1%)	0.427
No	8(34.8%)	5(25%)		11(39.3%)	15(42.8%)	
LDH <460	8(34.8%)	7(35%)	1.00	6(21.4%)	6(17.1%)	0.752
>460	15(65.2%)	13(65%)		22(78.6%)	29(82.8%)	
BM Involved	4(17.4%)	3(15%)	1.00	8(28.6%)	6(17.1%)	0.772
Not involved	19(82.6%)	17(85%)		20(71.4%)	29(82.8%)	
Bulk Yes	4(17.4%)	6(30%)	0.473	4(14.3%)	7(20%)	0.741
No	19(82.6%)	14(70%)		24(85.7%)	28(80%)	
IPI Low risk	14(60.8%)	12(60%)	1.00	18(64.3%)	23(65.7%)	1.00
High risk	9(39.1%)	8(40%)		10(35.7%)	12(34.2%)	
RT Yes	3(13.1%)	6(30%)	0.263	4(14.3%)	5(14.2%)	1.00
No	20(86.9%)	14(70%)		24(85.7%)	30(85.7%)	
PF =<2	13(56.5%)	12(60%)	1.00	23(82.1%)	27(77.1%)	0.758
>2	10(43.5%)	8(40%)		5(17.9%)	8(22.9%)	

Table:8 Clinical characteristics in IPI low risk and high risk subgroup

	IPI Low Risk n=66,(62.3%)			IPI High Risk n=40,(37.7%)		
Clinical features	**RCHOP n=32,(48.4%)**	**CHOP n=34,(51.6%)**	**p**	**RCHOP n=19,(47.5%)**	**CHOP n=21,(52.5%)**	**p**
Age >60 years	5(15.6%)	8(23.5%)	0.540	8(42.1%)	7(33.4%)	0.745
<60 years	27(84.3%)	26(76.5%)		11(57.9%)	14(66.6%)	
Sex Male	21(65.6%)	22(64.7%)	1.00	14(73.6%)	14(66.6%)	0.736
Female	11(34.4%)	12(35.3%)		5(26.4%)	7(33.4%)	
Stage I,II	20(62.5%)	21(61.7%)	1.00	00(00%)	2(9.5%)	1.00
III,IV	12(37.5%)	13(38.3%)		19(100%)	19(90.5%)	
B-symptom Yes	18(56.25%)	23(67.6%)	0.447	14(73.6%)	17(80.9%)	0.712
No	14(43.75%)	11(32.4%)		5(26.4%)	4(19.1%)	
LDH <460	12(37.5%)	12(35.2%)	0.797	17(89.4%)	20(95.2%)	0.596
>460	20(62.5%)	22(64.8%)		2(10.6%)	01(4.8%)	
BM Involved	5(15.6%)	3(8.8%)	0.469	07(36.8%)	8(38.0%)	1.00
Not involved	27(84.4%)	31(91.2%)		12(63.2%)	13(62.0%)	
Bulk Yes	2(6.2%)	7(20.5%)	0.151	6(31.5%)	6(28.5%)	1.00
No	30(93.8%)	27(79.5%)		13(68.5%)	15(71.5%)	
GCB	14(43.7%)	12(35.3%)	0.615	9(47.3%)	8(38.0%)	0.750
Non-GCB	18(56.3%)	22(64.7%)		10(52.6%)	13(62.0%)	
RT Yes	3(9.3%)	5(14.7%)	0.710	4(21.0%)	6(28.5%)	0.721
No	29(90.7%)	29985.3%)		15(79.0%)	15(71.5%)	
PF=<2	27(84.4%)	27(79.4%)	0.752	9(47.4%)	12(57.1%)	0.752
>2	5(15.6%)	7(20.6%)		10(52.6%)	9(42.9%)	

RESULTS

Patients clinical and biological characteristics (Table:5,6,7,8)

After applying afore mentioned inclusion and exclusion criteria, a total of 106 patients were included in the study. This comprises 71(67.0%) males and 35(33.0%) females with ratio approximately 2:1. The median age in RCHOP group was 53years (range: 20-76 years) and in CHOP group was 48years (range:21-79years) .Out of 106 patients 78(73.6%) patients were of younger age group (< 60 years) ,comprises 38(74.5%) patients in RCHOP and 40(72.7%) patients in CHOP group. The ECOG performance score was =<2 in 75(70.8%), the B-symptom was present in 72(67.9%) and the bone marrow was involved in 23(21.7%) of patients at diagnosis. 22(20.8%) cases has one or more extra-nodal involvement and bulk disease (size more than 10 cm) in 21(19.8%) of patients. In 80(75.5%) of cases the LDH level was above the normal level (460u/dl), comprises of 37(72.5%) patients in RCHOP group and 43(78.5%) patients in CHOP group. The haemoglobin value was <10gm% in 22(20.8%) of patients. CNS study was done in 29 patients and of one patients in CHOP group has involvement at diagnosis. As per hans .etalimmunomarkers classification the Germinal center B-cell like and non-germinal center B-cell like cases were 43(40.5%) and 63(59.5%) respectively in study population. In RCHOP group out of 51 patients, 23(45.1%) were GCB and 28(54.9%) patients were Non-GCB and in CHOP group out of 55 patients 20(36.3%) patients were GCB and 35(59.4%) patients were in Non-GCB group. All patients were scored as per international prognostic index. In RCHOP group out of 51 patients low(0,1), low intermediate(2), high intermediate(3) and high risks(4,5) were 15(29.4%), 17(33.3%), 12(23.5%) and 7(13.7%) patients respectively, and in CHOP group out of 55 patients 15(27.2%),19(34.5%),14(25.4%) and 7(12.7%) patients respectively. Out of 106 patients 66(62.2%) were in low risk(0,1,2) and 40(37.7%) were in high risk(3,4,5).

In RCHOP group low risk(0,1,2),high risk(3,4,5) were 32(62.7%),19(37.2%) and CHOP group 34(61.8%),21(38.1%) respectively. The patients characteristics were almost similar in RCHOP and CHOP groups and none of the p value were significant(significant $p<0.05$).The clinical characteristics of the patients were further analysed in two subgroups; IPI based low risk and high risk groups and immune-marker based Germinal center B-cell like and Non-germinal center B-cell like groups. The female patients 11(55%) were more compared to male patients 9(45%) in germinal center group patients who got CHOP chemotherapy ($p=0.06$).Other clinical characteristics distribution were similar in two groups of patients (non of the p value was significant).

TABLE: 9 Treatment

	Total	Group		p
		RCHOP	CHOP	
Chemotherapy	106	51	55	
Radiotherapy(consolidate)	18(17.0%)	7(13.7%)	11(20%)	0.179
CNS therapy(intra-thecal)*	16(15.1%)**	5(9.8%)**	11(20%)**	0.445

*At diagnosis:1(CHOP) and 0(RCHOP) had CNS disease
**Prophylactic intrathecal therapy

TABLE:10 Post chemotherapy status RCHOP(n:51), CHOP(n:55)

Response	After 3 cycle			After 6 cycle		
	RCHOP	CHOP	p	RCHOP	CHOP	p
Complete	32(62.7%)	24(43%)	0.079	45(88.2%)	39(70.9%)	
response(CR+CRU)	19(37.3%)	29(%)		1(1.9%)	6(10.9%)	
Parital response(PR)	0(0%)	2(3.6%)		2(3.92%)	7(12.7%)	0.082
Progressive disease(PD)				3(5.88%)	3(5.4%)	

TABLE:11 Status at last follow up (Mean follow-up 36 months)

Response	Status at last follow up		
	RCHOP(n:51)	CHOP(n:55)	p
Complete response(CR+CRU)	37(75.2%)	30(54.5%)	
Parital response(PR)	0	0	
Progressive disease(PD)	2(3.9%)	7(12.7%)	**0**.081
Stable disease(SD)	2(3.9%)	1(1.8%)	
Relapse	10(19.6%)	17(30.9%)	

Table:12 Status at the time of analysis

GROUP	Alive	Dead	Unknown
Total(n:106)	71(66.9%)	20(18.9%)	15(14.2%)
RCHOP(n:51)	37(72.5%)	7(13.7%)	7(13.8%)
CHOP(n:55)	34(61.8%)	13(23.6%)	8(14.6%)

Table:13Unknown patient status at last follow up

GROUP	Remission	Relapse	Months (since last follow)
Total(n:15)	8(53.3%)	7(46.6%)	
RCHOP(n:7)	7(100%)	0(00%)	(12-32months)
CHOP(n:8)	1(12.5%)	7(87.5%)	(17-40 months)

Chemotherapy and response (Table:9,10,11,12,13)

Patients received either six cycles of CHOP chemotherapy;55(51.8%) patients or Rituximab with CHOP chemotherapy;51(48.2%) patients. 7(13.7%) patients in RCHOP and 11(20%) patients in CHOP group received consolidative radiotherapy either due to bulk disease or residual disease at end of six cycle of chemotherapy. Total of 16(15.1%) patients received prophylactic intrathecal methotrexate (5;9.8% patients in RCHOP and 11;20% patients in CHOP group) though only one patient had documented CNS disease in CHOP group. The treatment response were analysed after three cycles and six cycles as complete response(CR+CRu), partial response(PR),stable disease(SD),Progressive disease(PD) and survival were analysed as relapse free survival(RFS),event free survival(EFS) and overall survival(OS). After three cycles of chemotherapy the CR+CRu in CHOP was inferior 24(43%0 vs 32(62.7%) in RCHOP group(p=0.7). After six cycle of chemotherapy in CHOP group, CR+CRu, PR, PD and SD were 39(70.9%),6(10.9%),7(12.7%)and 3(5.4%) respectively. It was better (p=0.08) in RCHOP treatment group as the CR+Cru, PR, PD and SD were 45(88.2%), 1(1.9%),2(5.88%) and 3(3.92%) respectively. At the time of analysis in CHOP group of patients the CR+CRu was 30(54.5%),PD was 7(12.7%), SD was 1(1.8%) and 17(30.9%) patients has relapsed. The patients treated with RCHOP, CR+CRu rate was better, (p=0.09) 37(75.2%) and relapse was less 10(19.6%). Out of 106 patients 71(66.9%) were alive, 20(18.8%) death and 15(14.3%) patients status was not known at the time of analysis. The subgroup analysis showed in RCHOP group 37(72.5%) alive,7(13.7%) dead and unknown status 7(13.7%) patients, and in CHOP group 34(61.8%)alive,13(23.6%) dead and unknown status 8(14.5%) patients. In analysis the unknown patients were taken as alive and censored at that point with the respective disease status.

Survival analysis in different subgroups

Outcome comparison of CHOP and RCHOP

32

Table:14 Overall survival (OS)

Group	12 months	24 months	36 months	p
RCHOP(n=51)	97.7%	78.4%	78.4%	0.190
CHOP(n=55)	86.3%	69.1%	69.1%	

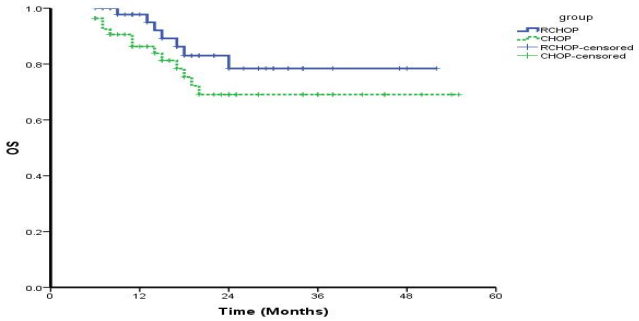


Fig: 3A Overall survival in 106 patients treated with CHOP and RCHOP

Table:15 Event Free Survival(EFS)

Group	12 months	24 months	36 months	p
RCHOP(n=51)	83.1%	73.4%	68.5%	0.190
CHOP(n=55)	76.2%	55.2%	47.9%	

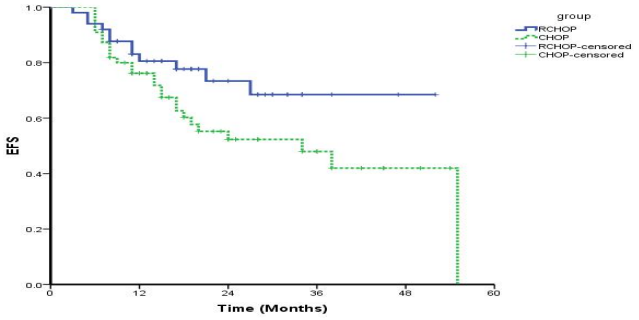


Fig: 3B Event free survival in 106 Patients treated with CHOP and RCHOP

Table:16 Cummulative RFS

Group	12 months	24 months	36 months	p
RCHOP(n=51)	80.5%	73.4%	68.5%	0.13
CHOP(n=55)	77.7%	55.7%	51.1%	

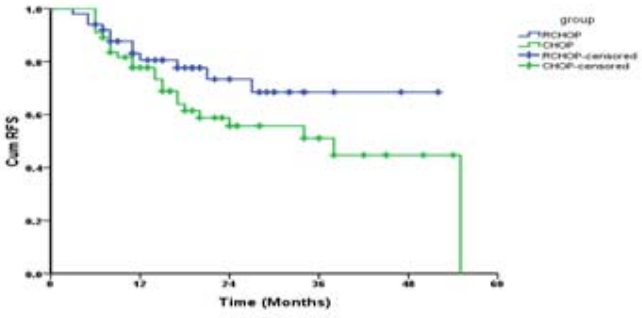


Fig: 3C Cumulative RFS in 106 patients Treated with CHOP and RCHOP

Analysis of response of CHOP and RCHOP chemotherapy:(Table:14,15,16 Fig:3 A,B,C)

At the median follow up of 36 months the cumulative Relapse free survival was 68.1% in RCHOP and 51.1% in CHOP group (p=0.139). The EFS was 73.4% vs 55.2% (p=0.07) and OS 78.4% vs 69.1% (p=0.19) respectively in RCHOP and CHOP group.

Table:17 Outcome comparison in clinical IPI risk groups(median follow up 24 months)

IPI Risk group		OS	P	EFS	P	RFS	P
Low Risk(0,1,2) (n=66)	RCHOP(n=32)	75.3%	0.26	75.1%	0.80	75.1%	0.29
	CHOP(n=34)	86.7%		72.5%		76.8%	
High Risk(3,4,5)(n=40)	RCHOP(n=19)	83.3%	0.004	74.9%	0.002	74.9%	0.002
	CHOP(n=21)	41.5%		19.8%		21.1%	

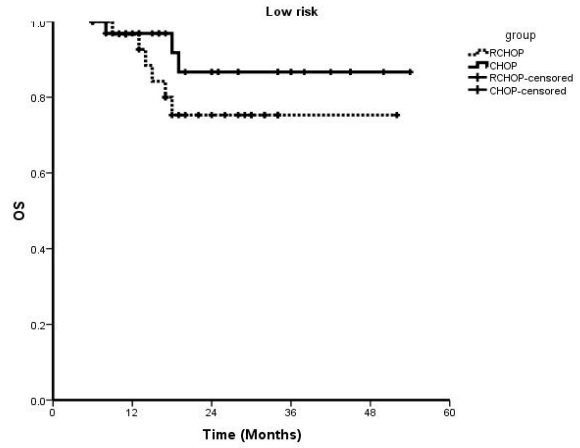


Fig 4A: Overall survival in 66 IPI low risk patients with CHOP and RCHOP

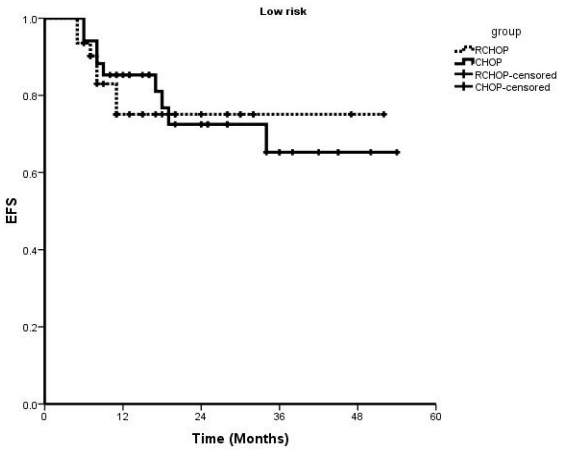


Fig 4B: Event Free survival in 66 IPI low risk patients with CHOP and RCHOP

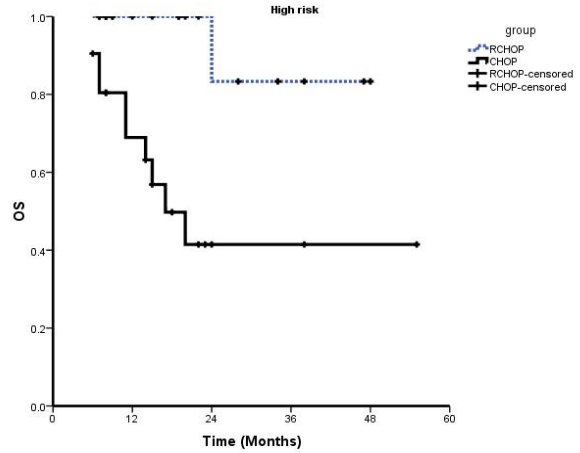


Fig 4C: Overall survival in 40 IPI high risk patients with CHOP and RCHOP

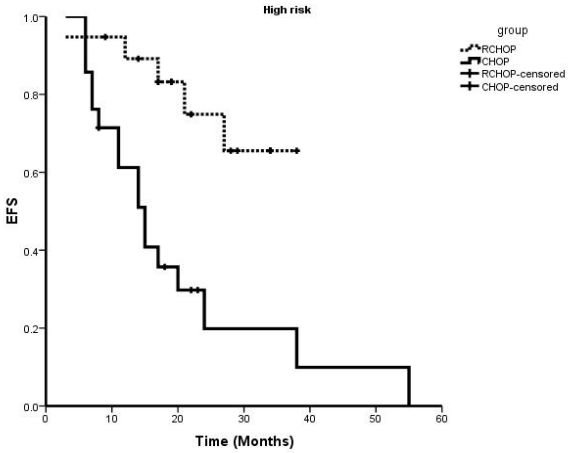


Fig 4D: Event Free Survival in 40 IPI high risk patients with CHOP and RCHOP

Analysis of response of chemotherapy in IPI risk subgroups : (Table:17 Fig:4 AB,C,D)

In low risk group(0,1,2) the OS, EFS and cumulative RFS at median follow-up of 24 months ,in RCHOP group of patients was 75.3%,75.1% and 75.1% ; and in CHOP group of patients was 86.7%,72.5% and 76.8% respectively(in low IPI risk group p=0.26 for OS, p=0.80 for EFS and p=0.29 for RFS). In highIPI risk group(3,4,5) the OS, EFS and cumulative RFS at median follow-up of 24 months ,in RCHOP group of patients was 83.3%,74.9% and 74.9% ; and in CHOP group of patients was 41.5%,19.8% and 21.1%% respectively(in high risk group was p=0.006 for OS, p=0.002 for EFS and p=0.002 for Cumulative RFS) . Patients who received CHOP chemotherapy the OS,EFS and RFS at median of 24 months was 86.7%,72.5% and 76.8% in low risk and 41.5%,19.8% and 21.1% respectively in high risk patients(p=0.001) and in RCHOP treated patients was 75.3%,75.1% and 75.1% in low IPI risk and 83.3%,74.9% and 74.9% respectively in high IPI risk patients(p=0.82) .

Outcome comparison GCB(n=43) and Non-GCB(n=63) groups(hans et.al)

Table:18 GCB treated with CHOP and RCHOP(median follow up 24 months)

Treatment GP	OS	EFS	RFS
RCHOP(n:23)	89.1%	80.2%	80.2%
CHOP(n:20)	50.3%	37.3%	46.3%
p	0.06	0.02	0.16

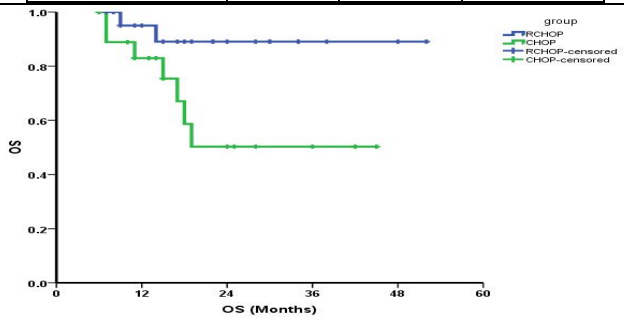


Fig 5A: Overall survival in 43GCB patients treated with CHOP and RCHOP

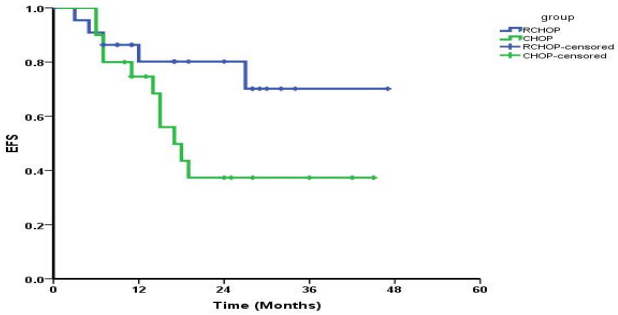


Fig 5B: Event free survival in 43GCB patients treated with CHOP and RCHOP

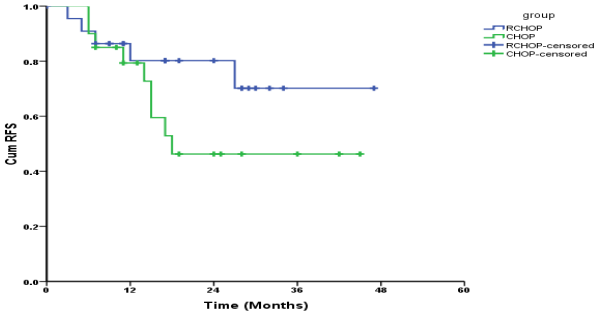


Fig 5C: Cumulative RFS in 43GCB patients treated with CHOP and RCHOP

Fig 5(A,B,C): Addition of rituximab to CHOP chemotherapy improved OS,EFS and Cumulative RFS in Germinal center B-cell like subgroup of nodal DLBCL patients.

Table:19 Non GCB treated with CHOP and RCHOP(median follow up of 24 months)

Treatment GP	OS	EFS	RFS
RCHOP(n:28)	69%	66.9%	66.9%
CHOP(n:35)	79.2%	60.6%	60.6%
p	0.8	0.4	0.4

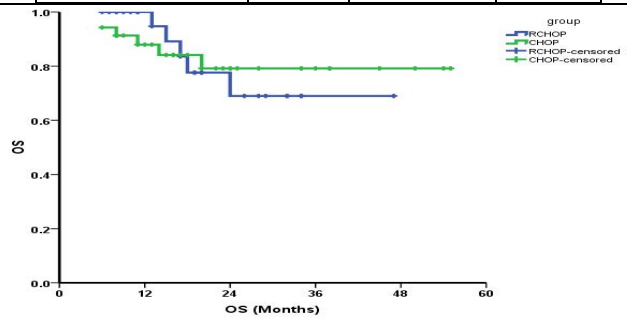


Fig 6A: Overall survival in 63 Non-GCB patients treated with CHOP and RCHOP

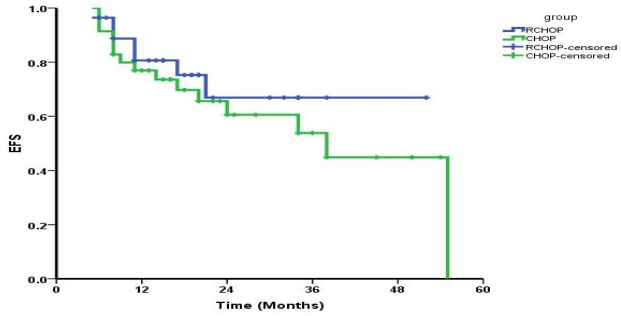


Fig 6B: Event free survival in 63Non-GCB patients treated with CHOP and RCHOP

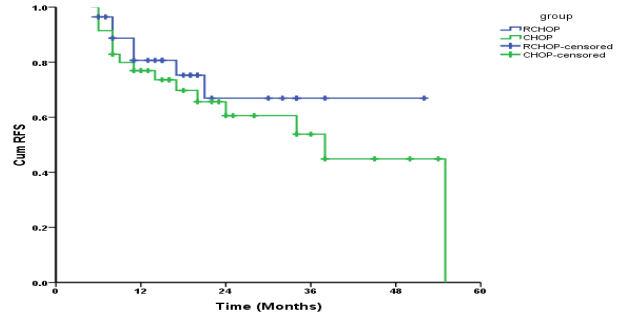


Fig 6C: Cumulative RFS in 63Non-GCB patients treated with CHOP and RCHOP

Fig 6(A,B,C): Addition of rituximab to CHOP chemotherapy improved OS,EFS and Cumulative RFS in Non-Germinal center B-cell like subgroup of nodal DLBCL patients.

Table:20 RCHOP in GCB and Non GCB(median follow up 24 months)

Treatment GP	OS	EFS	RFS
GCB(n:23)	89.1%	80.2%	80.2%
Non GCB(n:28)	69%	66.9%	66.9%
p	0.3	0.8	0.8

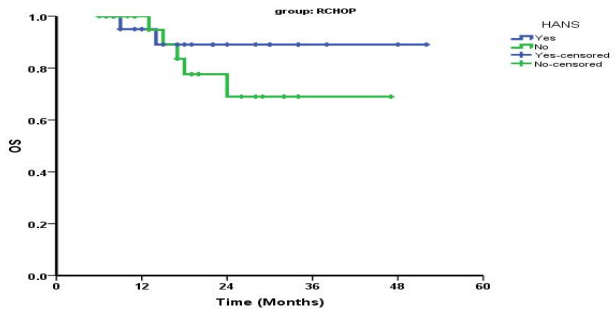


Fig 7A: Overall survival in 51 RCHOP treated patients in GCB and Non-GCB subgroup.

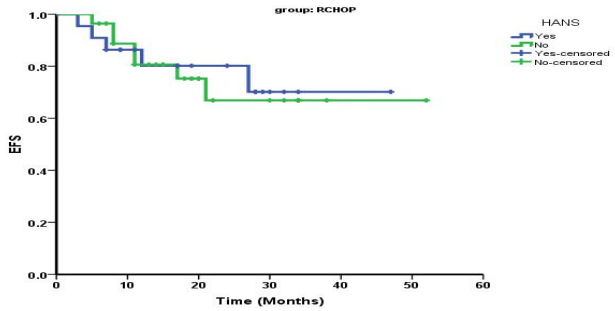


Fig 7B: Event free survival in 51 RCHOP treated patients in GCB and Non GCB subgroup.

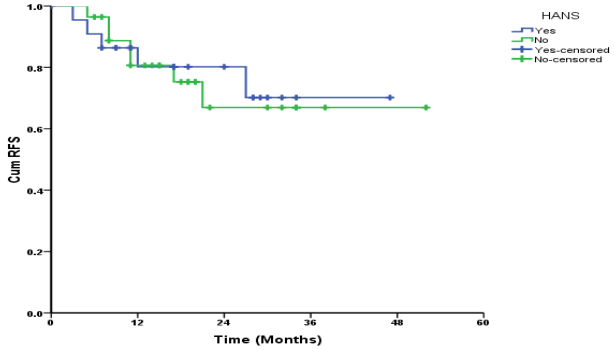


Fig 7C: Cumulative RFS in 51 RCHOP treated patients in GCB and Non GCB

Fig 7(A,B,C): Addition of rituximab to CHOP chemotherapy improved OS,EFS and Cumulative RFS in Germinal center B-cell and Non-Germinal center B-cell like subgroup of nodal DLBCL patients.

Response analysis of chemotherapy in GCB and Non-GCB subgroup (Table:18,19,20 Fig:5,6,7 A,B,C)

The Overall survival(OS), event free survival(EFS) and cumulative relapse free survival(RFS) at median follow up of 24 months were 71.8%,58.0%,63.4% in GCB vs 74.9%,66.3%,63.4% in non-GCB patients irrespective of different type of chemotherapy(p value not significant). In subgroup analysis the OS, EFS, and Cumulative RFS at median follow up of 24 months in GCB group were 89.1%,80.2% and 80.2% respectively in RCHOP chemotherapy treated patients vs 50.3%,37.3% and 46.3% respectively in CHOP chemotherapy treated patients,(OS p= 0.06,for EFS p=0.02 and for RFS p=0.16).The OS, EFS and Cumulative RFS at median follow up of 24 months in non-GCB group were 69.%,66.9% and 66.9% respectively in RCHOP chemotherapy treated patients vs 79.2%,60.6% and 60.6% respectively in CHOP chemotherapy treated patients,(OS p=0.81,for EFS p=0.41 and for RFS p=0.41).Patients who received RCHOP chemotherapy the OS,EFS and Cumulative RFS at median follow up of 24 months was 89.1 %,80.2% and 80.2% in GCB and 69%%,66.9%% and 66.9% respectively in Non-GCB patients (p value not significant). In CHOP treated patients the EFS and Cumulative RFS was 37.3% and 46.3% in GCB and 60.6% each in non-GCB patients,(p value not significant). The OS was 79.2% in non-GCB and 50.3% in GCB.

Table: 21 Chemotherapy related complication

Complication	Total no(%)	RCHOP	CHOP	p
Neutropenia	61(57.5%)	35(68.6%)	26(47.3%)	0.032
Hyperglycemia	26(24.5%)	14(27.5%)	12(21.8%)	0.652
Neuropathy	3(2.8%)	3(5.9%)	0	0.108
SIADH	6(5.7%)	5(9.8%)	1(1.8%)	0.103
DVT	3(2.8%)	2(4.1%)	1(1.8%)	

Chemotherapy complications(Table:21)

Neutropenia with or without fever was the commonest chemotherapy related complication in both the groups (68% in RCHOP and 47% CHOP p=0.032). The next common complication was hyperglycemia,(27.5% in RCHOP and 21.8% CHOP p=0.652). followed by neuropathy (5.9% in RCHOP and 0% CHOP p=0.108). and SIADH (9.8% in RCHOP and 1.8% CHOP p=0.103). Three patients has deep vein thrombosis most probably tumor related

DISCUSSION

Table:22 Incidence comparison of GCBvs non GCB with Litrature

Studies	Total number	GCB	Non-GCB
***Present**	***106***	***43(40.5%)***	***63(59.5%)***
**Hans,Blood 2004	152	64(42%)	88(58%)
**Nyman,Blood2007	194	97(50%)	97(50%)
**Kaifu JCO 2008	243	121(49.7%)	122(50.3%)
**Shiozawa,Leuk.R2007	248	71(29%)	177(71%)

*Denovo DLBCL nodal site only

**De novo DLBCL all sites

Table:23 Outcome comparison with Published literatures

Studies	No of patients		EFS*		OS*	
	RCHOP	CHOP	RCHOP	CHOP	RCHOP	CHOP
Present study *at 3 years	***51***	***55***	***68.5%***	***47.5%***	***78.5%***	***69%***
Coiffer.B*NEJM2002* *at 2 years	202	197	61%	43%	76%	63%
GELA *JCO2005* *at 5 years	197	202	47%	29%	58%	45%
B Columbia *JCO2005* *at 2 years	292	292	69%	51%	78%	42%
US intergp*JCO2006* *at 5 years	279	267	52%	35%	67%	58%
MINT trial *Lancet2006* *at 3 years	411	413	79%	59%	93%	84%

Discussion

Clinical and biological characteristics

A total of 106 patients of primary nodal diffuse large b cell lymphoma with age greater than 15 years were included in the study. This comprises 71(67.0%) males and 35(33.0%) females with ratio approximately 2:1[2,3,4] . The median age of the patients in our study was 53 years (range:20-76 years) in RCHOP group and 48 years(range:21-79 years) in CHOP group of patients. The median age reported in major western studies is in seventh decade. The median age of the group in SWOG 8516 trial ranged from 54-57 years which is comparable to our study[1].The B-symptom was present in 72(67.9%) and the bone marrow was involved in 23(21.7%) of patients at diagnosis. 22(20.8%) cases has one or more extra-nodal involvement other than the primary and bulk disease i.e greater than 10 cm on presentation in 21(19.8%) of patients. The published studies have quoted an incidence of 40% bulky disease and 40% initially confined extra-nodal disease [2,29]. Our study is on primary nodal disease so the above finding does not correlate with literature. In our study 80(75.5%) of cases has high LDH level (>460u/dl) comprises of 37(72.5%) patients in RCHOP group and 43(78.5%) patients in CHOP group. 22(20.8%) patients presented with anemia at diagnosis (Hb<10gm%) in . The LDH>ULN at diagnosis ranges from 30%-57% in MInT and RECOVER 60 trial.

In our study out of 106 patients 66(62.2%) were in low risk (0,1,2) and 40(37.7%) were in high risk(3,4,5). In RCHOP group low risk (0,1,2),high risk (3,4,5) were 32(62.7%),19(37.2%) and CHOP group 34(61.8%),21(38.1%) respectively. The frequency of IPI risk stratified groups correlates with the published data [23]. As per hans.etal immune-markers classification (based on CD10,BCL6 and MUM1) the nodal cases were categorised as Germinal center B-cell like and Non germinal center B-cell like and were 43(40.5%) and 63(59.5%) respectively.

In RCHOP group out of 51 patients, 23(45.1%) were GCB and 28(54.9%) patients were Non-GCB and in CHOP group out of 55 patients 20(36.3%) patients were GCB and 35(59.4%) patients were in Non-GCB group. In three major published western literature the frequency of distribution of GCB and Non-GCB in denovo DLBCL in all tissue is almost 50% in each group[21,23,24(Table:22)]and in asian population the published literature shows 30% and 70% respectively[(schiozawa,leukR2007)]. Our study is only on nodal cases with frequency of distribution of GCB and Non-GCB is 40% and 60 respectively correlates nearest to hans.etal needs gene expression profiling for confirmation[21].

Chemotherapy and response

Patients received either six cycles of CHOP chemotherapy;55(51.8%) patients or Rituximab with CHOP chemotherapy;51(48.2%) patients. 7(13.7%) patients in RCHOP and 11(20%) patients in CHOP group received consolidative radiotherapy either due to bulk disease or residual disease at end of six cycle of chemotherapy. Total of 16(15.1%) patients received prophylactic intrathecal methotrexate (5;9.8% patients in RCHOP and 11;20% patients in CHOP group) though only one patient had documented CNS disease in CHOP group.

After three cycles of chemotherapy the CR+Cru in CHOP was inferior 24(43%0 vs 32(62.7%) in RCHOP group (p=0.7) though p value not significant. After six cycle of chemotherapy in CHOP group, CR+Cru, PR, PD and SD were 39(70.9%), 6(10.9%), 7(12.7%)and 3(5.4%) respectively. It was better (p=0.08,) in RCHOP treatment group as the CR+Cru, PR, PD and SD were 45(88.2%),1(1.9%),2(5.88%) and 3(3.92%) respectively though the p value is not significant. At the mean follow up of 36 months the patients treated with RCHOP had CR+CRu rate better 37(75.2%) and relapse was less 10(19.6%) compared to CHOP chemotherapy(p=0.09).

The analysis shows trend (p value not significant) towards better CR rates after addition of Rituximab to CHOP chemotherapy and is comparable with the literature[32,33] At the median follow up of 36 months the cumulative RFS was 73.4% in RCHOP and 55.7% in CHOP group (p=0.139). The EFS was 73.4% vs 55.2% (p=0.07) and OS 78.4% vs 69.1% (p=0.19) respectively in RCHOP and CHOP group. The advantage of 21% in event free survival (EFS) and 10% in overall survival (OS) with addition of Rituximab to CHOP chemotherapy is comparable with the literature (Table:23).

In low risk IPI group(0,1,2) the OS, EFS and cumulative RFS at median follow-up of 24 months ,in RCHOP group of patients was 75.3%,75.1% and 75.1% ; and in CHOP group of patients was 86.7%,72.5% and 76.8% respectively(p value not significant).The OS is better in CHOP group most likely due poor follow up in relapse group of patients. In high IPI risk group(3,4,5) the OS, EFS and cumulative RFS at median follow-up of 24 months ,in RCHOP group of patients was 83.3%,74.9% and 74.9% ; and in CHOP group of patients was 41.5%,19.8% and 21.1%% respectively(high IPI risk group p=0.006 for OS, p=0.002 for EFS and p=0.002 for RFS) . Patients who were treated with only CHOP chemotherapy did bad in high IPI risk group with OS, EFS 41.5%,19.8% compared to low risk 86.7%,72.5% (p=0.001). Addition of Rituximab improves the OS, EFS 83.3%,74.9% in high risk comparable with the low risk 75.3%,75.1% (p=0.28).The advantage of Rituximab in high risk IPI nodal DLBCL correlates with published literature [23,29,36,37].

The Overall survival(OS), event free survival(EFS) and Cumulative relapse free survival(RFS) at median follow up of 24 months in GCB group were 89.1%,80.2% and 80.2% respectively in RCHOP chemotherapy patients vs 50.3%,37.3% and 46.3% respectively in CHOP chemotherapy patients,(OS p=0.06,for EFS p=0.02 and for RFS p=0.16).The survival correlates with Kai Fu JCO[23]2008 paper which showed addition of Rituximab in GCB improves survival significantly.

In non-GCB group OS,EFS and Cumulative RFS were 69.%,66.9% and 66.9% respectively in RCHOP chemotherapy patients vs 79.2%,60.6% and 60.6% respectively in CHOP chemotherapy patients,(OS p=0.81,for EFSp=0.41 and for RFS p=0.41).It does not correlates with literature[23] and this my be because of selection bias in this study and short follow-up, though there is minimal advantage in EFS and Cumulative RFS with Rituximab addition. Patients who received RCHOP chemotherapy the OS,EFS and Cumulative RFS at

median follow up of 24 months was 89.1 %,80.2% and 80.2% in GCB and 69%%,66.9%% and 66.9% respectively in Non-GCB patients(p=0.3). Addition of Rituximab improves survival more in GCB than non-GCB, though p value not significant correlates with Kai Fu JCO[23]2008 paper, but not with Nyman Blood[24] 2008 which showed addition of Rituximab negates the survival advantage of GCB over Non-GCB.

Neutropenia with or without fever was the commonest chemotherapy related complication in both the groups (68% in RCHOP and 47% CHOP p=0.032). The frequency of neutropenia in Rituximab treated patients similar to international literature[32].The next common complication was hyperglycemia, followed by neuropathy and SIADH .

CONCLUSION

Conclusion

1) The frequency of distribution of Germinal centre(GCB) and non-Germinal centre(non-GCB) in nodal DLBCL cases in our population is 40% and 60% respectively(Table:3).
2) The frequency of distribution of low IPI risk (0,1,2) and high IPI risk(3,4,5) in nodal DLBCL cases in our population is 62% and 37.7%% respectively.
3) Addition of Rituximab to CHOP chemotherapy improves event free survival by 20% and overall survival by 10% in our patients comparable to published literature (Table:14).
4) Addition of Rituximab to CHOP chemotherapy significantly improves overall survival in GCB and high IPI risk group comparable to published litratures.
5) In non-GCB and IPI low risk groups the Rituximab improves the event free survival and relapse free survival but not the overall survival.
6) Neutropenia with or without fever was the most common chemotherapy related toxicity significantly more in Rituximab group comparable to published litratures.

Limitation of study

1) It is a retrospective study.
2) Selection bias; only nodal cases with minimum six months follow up patients selected.
3) DLBCL Classification based on cell of origin (GCB and non GCB) by three immunomarkers has its own limitations.
4) Short follow up and follow status of the few patients at the time of analysis not known.
5) Small sample size.

PROFORMA

PROFORMA:

Title:Diffuse Large B cell Lymphoma Single centre study

Sl.No:

Name: Hospital No: Sex: Age:

Date of diagnosis:

At diagnosis: Haemoglobin: Total leucocyte count: Platelet count: LDH:

Viral serology (HIV, HbSAg, HCV):

Nodal(Site):

Extranodal(Site):

B symptoms:

Immunomarkers

Markers	CD10	BCL6	MUM1	CD20	**Impression**
+/-					**GC/nonGC/unclassified**

Bone marrow aspirate and biopsy

Ann Arbor staging:

Performance score (ECOG):

International prognostic index (score):

Radiology: At diagnosis

After three cycles of chemotherapy

After six cycles of chemotherapy

At follow-ups

CSF examination:

Chemotherapy Protocol:

CHOP Chemotherapy	
Rituximab CHOP chemotherapy	

i

Chemotherapy cycles date:

First cycle	
Sixth cycle	

Radiotherapy:

Intrathecal CNS therapy:

Response:

After three cycles	
After six cycles	
At last follow up	
Relapse date and site	

Complication during treatment:

Neutropenia	
Hyperglycemia	
Neuropathy	
SIADH	
Others	

BIBLIOGRAPHY

Bibliography

1.Jaffe ES .The 2008 WHO classification of lymphoma:implications for clinical practice and translational research. Hematol Am SocEduc Program.2009:523-531

2.Distribution of various subtypes of non-Hodgkin's lymphoma in India:A study of 2773 lymphomas using R.E.A.L. and WHO Classifications K. N. NareshAnnals of Oncology 11(Suppl I):S63-S67 2000

3.Diffuse large Bcell Lymphoma :experience from tertiary care center in north india . KherR ,L.AIMMSDept of Medical oncologyMed Oncology 2009 April 7

4. Fisher RI, Miller TP, O'Connor OA. Diffuse aggressive lymphoma. Hematology (Am SocHematolEduc Program). 2004:221-236.

5.Friedberg JW, Fisher RI. Diffuse large Bcell lymphoma. HematolOncolClinNorthAm. 2008;22:941-952, ix.

6.Fisher SG .The emerging concept of antigen drivenlymphomas:epidemiology and treatment implications.CurrentopinOncol 2006:18(5):4117-24.

7.Christopher R. Improving outcome for patients with diffuse large B cell lymphoma CA Cancer J Clin 2010;60;3939-408.

8. Morton LM, Wang SS, Cozen W, et al. Etiologic heterogeneity among non- Hodgkin lymphoma subtypes. Blood. 2008;112:5150-5160.

9. A predictive model for aggressive non-Hodgkin lymphoma. The Int. Non-Hodgkin Lymphoma Prognostic Factors Project. N Engl J Med. 1993;329:987-994.

10.Sehn LH, Berry B, Chhanabhai M, et al. The Revised International Prognostic Index (R-IPI) is a better predictor of outcome than the Standard IPI.for patients with DLBCL treated with R-CHOP. Blood. 2007;109:1857-1861.

11.Sehn LH, The revised International Prognostic Index(R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with RCHOP .Blood. 2007;109: 1857-1861.

12.Maritaziepert; Standard International Prognostic Index Remains a Valid predictor of outcome for patients with aggressive CD20+B-cell Lymphoma in Rituximab Era. JCO;May,volume28,2010 page;2373-2380.

13. JuweidME,et al. Use of positron emission tomography for response assessment of lymphoma: consensus of the Imaging Subcommittee of International Harmonization Project in Lymphoma. J ClinOncol. 2007;25:571-578.

14. Spaepen K, Stroobants S, Dupont P, et al. Early restaging positron emission tomography with (18)F-fluorodeoxyglucosepredictsoutcome in patients with aggressive non-Hodgkin lymphoma. Ann Oncol. 2002;13:1356-1363.

15.49. Itti E, Lin C, Dupuis J, et al. Prognostic value of interim 18F-FDG PET in patients with diffuse large B-Cell lymphoma: SUV based assessment at 4 cycles of chemotherapy. J Nucl Med. 2009;50:527-533.

16. RosenwaldAet al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma.NEJMed.2002;346:1937-1947.

17. Rosenwald A, Wright G, Leroy K, et al. Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup of diffuse large B cell lymphoma related to Hodgkin lymphoma. J Exp Med. 2003;198:851-862.

18. Iqbal J, Greiner TC, Patel K, et al. Distinctive patterns of BCL6 molecular alterations and their functional consequences in different subgroups of diffuse large B-cell lymphoma. Leukemia. 2007;21:2332-2343.

19. Iqbal J, Neppalli VT, Wright G, et al.BCL2 expression is a prognostic marker for the activated B-cell-like type of diffuse large B-cell lymphoma. J ClinOncol. 2006;24:961-968.

20. Iqbal J, Sanger WG, Horsman DE, et al.BCL2 translocation defines a unique tumor subset within the germinal center B-cell-like diffuse large B-cell lymphoma. Am JPathol. 2004;165:159-166.

21. Hans CP, Weisenburger DD, Greiner TC,et al. Confirmation of the molecular classification of diffuse large B-cell lymphoma by immune-histochemistry using a tissue microarray. Blood. 2004;103:275-282.

22. Choi WW, Weisenburger DD, Greiner TC,et al. A new immunostain algorithm classifies diffuse large B-cell lymphoma into molecular subtypes with high accuracy. Clin Cancer Res. 2009;15:5494-5502.

23. Addition of Rituximab to Standard Chemotherapy Improves the Survival of Both the Germinal Center B-Cell–Like and Non–Germinal Center B-Cell–Like Subtypes of Diffuse Large B-Cell Lymphoma Kai Fu, Dennis D. Weisenburger J ClinOncol 26:4587-4594. © 2008

24.HeidiNyman,Sirpa;Prognostic impact of immunohistochemically defined germinal center phenotype in diffuse large B-cell lymphoma patients treated with immune-chemotherapy. Blood,1,June2007.Vol109.

25.Mounier N, Briere J, Gisselbrecht C, et al: Rituximab plus CHOP (R-CHOP)overcomes bcl-2 associated resistance to chemotherapy in elderly patients with diffuse large B-cell lymphoma.Blood 2003;101;4279

26. Winter JN, Weller EA, Horning SJ, et al: Prognostic significance of bcl-6 protein expression in DLBCL treated with CHOP or R-CHOP:A prospective correlative stud y *Blood* 2006; 107:4207.

27.Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin lymphoma. N Engl J Med. 1993;328:1002-1006.69.

28.McKelvey EM, Gottlieb JA, Wilson HE,et al. Hydroxyldaunomycin (doxorubicin (Adriamycin)) combination chemotherapy in malignant lymphoma. Cancer. 1976;38:1484-1493.

29. Coiffier B. Diffuse large cell lymphoma.CurrOpinOncol. 2001;13:325-334.

30. Coiffier B, Haioun C, Ketterer N, et al. Rituximab (anti-CD20 monoclonal antibody)for the treatment of patients with relapsing or refractory aggressive lymphoma: a multicenter phase 2 study. Blood. 1998;92:1927-1932.

31. Coiffier B, Lepage E, Herbrecht R, etal.Mabthera (Rituximab) plus CHOP is superior to CHOP alone in elderly patients with diffuse large-B-cell lymphoma (DLCL): Interim results of a randomized GELA trial (abstract). Blood. 2000;96:223A. Abstract 950.

32. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med. 2002;346:235-242.

33. Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Grouped'Etude des Lymphomesdel'Adulte. J ClinOncol. 2005;23:4117-4126.

34. Coiffier B, Feugier P, Mounier N, et al. Long-term results of the GELA study comparing R-CHOP and CHOP chemotherapy in older patients with diffuse large B-cell lymphoma show good survival in poor-risk patients the GELA. J ClinOncolASCOAnnual Meeting Proceedings Part I. 2007; 25(18s). Abstract 8009.

35.Coiffier B. Long-term results of patients in the LNH-98.5 trial,the first randomized study comparing rituximab –CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Grouped'Etude des Lymphomesdel'Adulte. Blood 2010 116:2040-2045

36.Habermann TM, Weller EA, Morrison VA, et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J ClinOncol. 2006;24:3121-3127.

37.Pfreundschuh M, Trumper L, Osterborg A, et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomized controlled trial by the Mab-TheraInternationalTrial (MInT) Group. Lancet Oncol.2006; 7:379-391.

38.Zelenetz AD, Abramson JS, AdvaniRH,et al. NCCN clinical practice guidelines in oncology: non-hodgkin lymphoma. J NatlComprCancNetw. 2010;8:288-334.

39. Philip T, Guglielmi C, Hagenbeek A, et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin lymphoma. N Engl J Med. 1995; 333:1540-1545.

40. Vose JM, Zhang MJ, Rowlings PA, et al. Autologous transplantation for diffuse aggressive non-Hodgkin lymphoma inpatients never achieving remission: a report from the Autologous Blood and Marrow Transplant Registry. J ClinOncol. 2001;19:406-413.

41. Oliansky DM, Czuczman M, Fisher RI,et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the treatment of diffuse large B-cell lymphoma: update of the 2001 evidence-based review. Biol Blood Marrow Transplant.[Publishedonline ahead of print Jul 22 2010. PMID:20656046]

42. Gisselbrecht C, Glass B, Mounier N, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J ClinOncol.[Published online ahead of print Jul 262010. PMID: 20660832].

43. Gisselbrecht C, Glass B, Mounier N, et al. R-ICE versus R-DHAP in relapsed patients with CD20 diffuse large B-cell lymphoma(DLBCL) followed by autologous stem cell transplantation: CORAL study(abstract). J ClinOncol. 2009;27(suppl 15).Abstract 8509.

44. Leonard JP, Martin P, BarrientosJ,Elstrom R. Targeted treatment and new agentsin diffuse large B-cell lymph.SeminHematol. 2008;45(suppl 2):S11-S16.

45. Friedberg JW, Sharman J, SweetenhamJ,et al. Inhibition of Syk with fostamatinibdi sodium has significant clinical activity in non-Hodgkin lymphoma and chronic lymphocytic leukemia. Blood. 2010;115:2578-2585.

46. Fisher RI, Bernstein SH, Kahl BS, et al. Multicenter phase 2 study of bortezomib inpatients with relapsed or refractory mantle cell lymphoma. J ClinOncol. 2006;24:4867-4874.

47. Dunleavy K, Pittaluga S, CzuczmanMS,et al. Differential efficacy of bortezomib plus chemotherapy within molecular subtypes of diffuse large B-cell lymphoma Blood. 2009;113: 6069-6076.

48. Furman RR, Martin P, Ruan J, et al. Phase1 trial of bortezomib plus R-CHOP in previously untreated patients with aggressive non-Hodgkin lymphoma. Cancer. [Publishedonline ahead of print Jul 27 2010.PMID: 20665890]

49. Leonard JP, Furman RR, Cheung Y-KK,et al. CHOP-R þ bortezomib as initial therapy for diffuse large B-cell lymphoma(DLBCL) (abstract). J ClinOncol 2007ASCO Annual Meeting Proceedings Part I.2007;25(18S):8031.

50. Robertson MJ, Kahl BS, Vose JM, etal.Phase 2 study of enzastaurin, a protein kinase C beta inhibitor, in patients with relapsed or refractory diffuse large B-cell lymphoma. J ClinOncol. 2007;25:1741-1746.

51.Wiernik PH, Lossos IS, Tuscano JM, et al.Lenalidomidemonotherapy in relapsed or refractory aggressive non-Hodgkin lymphoma.JClinOncol. 2008;26:4952-4957.

52. Nowakowski GS, LaPlant B, HabermannT,et al. A phase I/II Trial of lenalidomideandrchop (r2chop) in patients with newly diagnosed diffuse large B -Cell (DLBCL) and follicular grade 3 lymphoma (abstract). Blood.(ASH). 2009;114.Abstract 1669.

53. Micallef IN, Kahl BS, Maurer MJ, et al. Apilot study of epratuzumab and rituximabin combination with cyclophosphamide, doxorubicin, vincristine, and prednisone chemotherapy in patients with previouslyuntreated, diffuse large B-cell lymphoma.

54.Addition of Rituximab to Standard ChemotherapyImproves the Survival of Both the Germinal CenterB-Cell–Like and Non–Germinal Center B-Cell–LikeSubtypes of Diffuse Large B-Cell LymphomaKai Fu, Dennis D. Weisenburger J ClinOncol 26:4587-4594. ©

MASTER SHEET

IPI RISK GROUP Low Risk(0,1):1 Low Inter(2):2 High Inter(3):3 High Risk(4,5):4 Low Risk(0,1,2):1 High Risk(3,4,5):2 **Hans** GCB:1 Non-GCB:2 **LDH** <460U/dl:1 >460U/dl:2	**Sex** Male:1 Female:2 **Age** <60 years:1 >=60 years:2 **B-symptom** Yes:1 No:1 **CNS** Involved:1 Not involved:2 Not done:3	**Stage** I,II:1 III,IV:2 **Extra-nodal** Yes:1 No:2 **Performance score** =<2:1 >:2 **Bulk disease** Yes:1 N:2	**Bone-marrow** Involved:IN Not involved:NI **Response to therapy** Complete response:1 Complete response unconfirmed :1 Partial Response:2 Progressive disease:3 Stable disease:4 Relapse:5

Coding for the master sheet

CHOP GROUP

S.NO	Age	Sex	Date of Dx	Site involved	Bulk	Extranodal	B symp	Performance	HB	CNS	Bone Marrow	LDH	Stage	IPI	HANS	First Cycle	Mid Course
1	31	M	1/4/2006	Cervical	2	2	1	1	13.7	2	NI	719	IIB	1	2	1/9/2006	1
2	27	M	3/6/2006	Cervical	2	1	2	1	14.2	3	NI	978	IIIBE	3	2	3/14/2006	1
3	30	F	4/29/2006	Cervical	1	2	1	1	7.6	3	NI	571	IIIBXS	3	1	5/4/2006	2
4	44	M	11/24/2008	Cervical	2	2	1	1	9.9	2	NI	491	IIIB	2	2	11/28/2008	2
5	44	M	5/31/2006	Cervical	2	1	1	3	10.6	3	NI	911	IVBE	3	1	6/17/2006	4
6	79	M	4/28/2006	cervical	2	2	1	3	11.4	3	NI	441	IIIB	3	2	5/9/2006	1
7	46	M	5/19/2006	Abdomen	2	2	1	2	11.8	3	NI	906	IVBS	3	2	6/9/2006	2
8	32	M	7/4/2006	Abdomen	1	2	2	1	6.7	3	IN	898	IVBX	4	2	7/7/2006	2
9	21	M	8/31/2005	Abdomen	1	2	1	2	8.4	3	IN	1646	IVBX	4	2	9/29/2005	2
10	63	M	1/31/2007	Axilla	2	2	2	1	14.1	3	NI	566	IIIA	3	2	2/21/2007	1
11	64	M	3/26/2007	inguinal	2	1	1	2	8.1	2	IN	939	IVBE	5	2	4/12/2007	2
12	35	F	4/25/2007	Abdomen	2	2	1	1	6.8	2	NI	994	IIIBS	2	2	5/1/2007	1
13	56	M	5/2/2007	Abdomen	2	1	1	3	12.6	2	NI	463	IIBE	3	1	5/4/2007	2
14	61	F	7/7/2007	Abdomen	1	2	1	2	10.4	3	NI	636	IIBX	3	1	8/28/2007	2
15	39	F	8/3/2007	Inguninal	2	2	1	1	11.7	2	NI	610	IIB	2	2	8/22/2007	1
16	47	M	10/29/2007	Cervical	1	2	1	1	11.6	2	NI	935	IIIBX	2	2	11/3/2007	2
17	40	M	12/20/2007	cervical	2	2	2	0	15.5	3	NI	531	IIA	1	1	1/3/2008	1
18	48	F	15/1/2008	Cervical	2	2	1	2	5.3	3	IN	1804	IVBS	4	1	2/29/2008	2
19	40	F	5/1/2008	Cervical	2	2	1	1	10.6	3	NI	614	IIIB	3	2	5/6/2008	1
20	54	F	6/5/2008	Cervical	2	2	1	0	11.8	3	NI	509	IIB	1	1	7/1/2008	2
21	52	M	6/19/2008	Cervical	1	2	1	1	12	3	NI	686	IIIBXS	2	1	7/1/2008	1
22	66	M	6/9/2008	Inguinal	2	2	2	2	11.7	3	NI	710	IIA	2	2	6/11/2008	2
23	62	M	9/24/2008	Cervical	1	2	1	1	7.4	3	NI	939	IIIBX	3	1	9/30/2008	2
24	40	M	10/6/2008	Cervical	1	2	1	1	9.9	3	NI	1570	IIIBX	3	2	10/18/2008	2
25	32	F	11/22/2008	inguinal	2	2	1	1	9.1	3	NI	2260	IVB	3	2	12/5/2008	2
26	63	M	1/22/2009	Axilla	1	2	1	1	12.8	3	NI	664	IIBX	2	2	2/3/2009	2
27	51	M	4/17/2009	Cervical	2	2	2	0	13.6	2	NI	556	IIA	1	2	4/29/2009	1

S.NO	Date of Compleltion	CNStherapy	Radiotherapy	Status post six cycle	Date LFU	Months	Status LFU	Relapse	Site	Month CR	Alive	Lost follow	Neutrope	Hyperrgly	Neuro	SIADH	Others
1	4/25/2006	2	2	1	2/22/2010	49.6	1	No	No	49.6	1	2	2	2	2	2	
2	6/26/2006	2	2	1	5/2/2009	37.9	5	8/1/2008	Node	28.9	2	2	2	2	2	2	
3	8/29/2006	2	1	1	7/27/2007	14.9	5	4/27/2007	Node	11.9	2	2	2	2	2	2	
4	3/13/2009	2	2	3	12/17/2010	24.7	3	No	No	24.7	1	2	2	2	2	2	
5	9/8/2006	2	2	4	8/14/2007	14.5	4	10/24/2006	Marrow	4.8	2	2	1	2	2	2	
6	9/8/2006	2	2	1	12/7/2007	19.3	5	3/26/2007	Node	10.9	2	2	1	1	2	2	
7	2/16/2007	2	2	1	11/22/2010	54.1	5	3/20/2007	Node	10.0	1	2	2	2	2	2	
8	11/10/2006	2	2	4	1/10/2007	6.2	4	10/11/2006	Node	3.3	2	2	1	2	2	2	
9	1/6/2006	2	1	2	10/23/2006	13.7	5	9/21/2006	Node	12.7	2	2	1	2	2	2	
10	6/6/2007	2	2	1	1/27/2009	23.9	5	8/14/2008	Node	18.4	2	2	2	2	2	2	
11	7/26/2007	2	2	2	2/12/2008	10.6	5	1/31/2008	Skin	10.2	2	2	1	1	2	2	
12	8/21/2007	2	2	1	1/11/2008	8.6	5	1/10/2008	Node	8.6	2	2	2	2	2	2	
13	11/6/2007	2	1	3	9/17/2008	16.6	4	9/17/2008	Spine	16.6	2	2	2	2	2	2	
14	12/26/2007	2	2	1	6/9/2008	11.1	5	6/9/2008	Node	11.1	2	2	1	2	2	2	
15	12/14/2007	2	2	1	9/17/2010	37.5	1	No	No	37.5	1	2	2	2	2	2	
16	2/19/2008	2	2	1	8/3/2010	33.1	1	No	No	33.1	1	2	2	2	2	2	
17	4/19/2008	2	2	1	12/15/2010	35.8	1	No	No	35.8	1	2	2	2	2	2	
18	5/13/2008	1	1	4	7/10/2008	6.2	4	6/25/2008	Node	5.2	2	2	1	2	2	2	
19	8/22/2008	2	2	1	3/24/2010	23	1	No	No	23.0	1	2	1	2	2	2	
20	12/1/2008	2	2	2	12/9/2009	18.1	5	2/25/2009	Node	8.7	1	1	2	2	2	2	
21	10/14/2008	2	1	1	10/5/2010	24.5	1	No	No	24.5	1	2	2	2	2	2	
22	10/1/2008	2	2	2	1/30/2009	7.7	4	30/1/2009	No	7.7	1	1	2	2	2	2	
23	2/13/2009	2	2	1	4/13/2009	6.6	1	No	No	5.6	1	1	1	2	2	2	T B
24	2/3/2009	2	2	1	8/10/2010	22.1	1	No	No	22.1	1	2	1	2	2	2	
25	3/20/2009	2	2	4	5/29/2009	6.2	5	5/29/2009	Node	6.2	1	1	2	2	2	2	
26	7/2/2009	2	2	1	2/2/2010	12.4	1	No	No	12.4	1	2	1	2	2	2	
27	9/1/2009	2	1	1	8/6/2010	15.6	1	No	No	15.6	1	2	2	2	2	2	

S.NO	Age	Sex	Date of Dx	Site involved	Bulk	Extranodal	B symp	Performance	HB	CNS	Bone Marrow	LDH	Stage	IPI	HANS	First Cycle	Mid Course
28	60	M	6/1/2009	Cervical	2	2	1	0	10.5	3	IN	1144	IVB	4	2	6/7/2009	1
29	45	F	7/20/2009	Cervical	2	2	2	1	11.9	3	NI	636	IIIA	2	2	7/31/2009	2
30	34	F	11/21/2009	Cervical	2	1	1	0	11.2	3	NI	940	IIBE	2	2	12/4/2009	1
31	68	F	12/23/2009	Cervical	2	1	1	1	12.8	3	NI	1017	IIIBE	2	1	1/11/2010	1
32	36	M	3/31/2010	Inguinal	2	2	1	1	11.7	3	IN	980	IVB	3	2	4/2/2010	2
33	59	M	9/14/2009	Cervical	2	2	1	1	12.4	3	IN	483	IVB	4	2	9/16/2010	2
34	69	F	4/23/2007	Cervical	2	2	2	1	8.7	3	IN	567	IVB	4	1	5/3/2007	4
35	33	F	3/10/2007	Abdomen	1	2	1	2	6.7	3	NI	2335	IIIBX	2	1	4/6/2007	2
36	49	F	4/14/2007	Ingunal	1	1	1	3	6.7	3	NI	391	IIIBX	2	1	4/23/2007	2
37	41	M	9/11/2008	Nasophyx	2	2	2	1	14.5	2	NI	490	IIA	1	2	9/26/2008	1
38	58	M	9/4/2009	Abd flank	1	1	2	3	15.1	3	NI	2410	IIBE	2	2	9/22/2009	2
39	63	M	3/4/2006	Ingunal	2	2	1	1	13.1	3	IN	395	IVB	2	2	3/15/2006	2
40	61	M	1/3/2006	Nasophyx	2	2	1	1	15.5	2	NI	245	IIB	1	2	1/16/2006	2
41	53	M	9/28/2009	Cervical	2	2	1	1	14.3	2	IN	1102	IVB	2	2	9/29/2009	2
42	47	F	5/28/2009	Cervical	2	1	1	2	12.3	2	NI	681	IIIBE	3	1	5/29/2009	2
43	46	M	9/15/2009	Cervical	2	1	2	2	16	2	NI	340	IIIB	2	1	9/17/2009	2
44	22	F	10/27/2008	Tonsil	2	1	1	0	10.7	2	NI	327	IBE	0	2	11/8/2008	1
45	39	M	11/3/2008	Tonsil	2	1	1	1	15.6	2	NI	305	IIBE	1	1	11/24/2008	1
46	40	M	8/25/2009	Tonsil	2	1	1	1	13.7	2	NI	388	IBE	0	2	8/27/2009	1
47	55	F	10/15/2008	Tonsil	2	1	2	1	11.5	2	NI	460	IAE	0	1	11/3/2008	1
48	37	M	4/22/2006	Tonsil	1	1	1	2	13.8	2	NI	962	IIBX	1	2	5/1/2006	2
49	39	F	12/4/009	Tonsil	2	1	2	0	13.7	2	NI	463	IAE	0	1	12/9/2009	1
50	67	M	9/18/2009	Tonsil	2	1	1	1	12.8	2	NI	441	IAE	1	1	9/23/2009	1
51	60	M	4/18/2006	Tonsil	2	1	2	1	11.5	2	NI	551	IAE	2	2	4/29/2006	1
52	57	M	8/26/2008	Axilla	2	2	1	1	12	3	NI	553	IIIB	2	2	9/2/2008	2
53	54	M	4/30/2007	Nasophyx	2	2	1	1	15.3	2	IN	362	IVB	1	1	5/8/2007	1
54	53	F	1/19/2008	Nasophyx	2	2	2	1	13.1	3	NI	335	IIA	1	2	2/22/2008	1
55	69	M	1/27/2009	Nasophyx	2	2	1	2	12.9	2	NI	971	IIB	2	2	2/28/2009	1

S.NO	Date of Compleltion	CNStherapy	Radiotherapy	Status post six cycle	Date LFU	Months	Status LFU	Relapse	Site	Month CR	Alive	Lost follow	Neutropepe	Hyperrgly	Neuro	SIADH	Others
28	9/22/2009	2	2	1	11/11/2010	17.3	1	No	No	17.3	1	2	2	2	2	2	
29	11/27/2009	2	2	4	3/2/2010	7.4	4	12/29/2009	Node	2.3	1	2	2	2	2	2	
30	3/23/2010	2	2	1	10/12/2010	10.7	1	No	No	10.7	1	2	2	2	2	2	
31	5/10/2010	2	2	1	11/10/2010	10.6	1	No	No	10.6	1	2	1	2	2	2	
32	7/30/2010	2	1	1	12/3/2010	8.1	1	No	No	8.1	1	2	2	2	2	2	
33	1/7/2010	2	1	2	5/13/2010	7.9	4	2/7/2010	Node	4.8	1	2	1	2	2	2	
34	6/10/2007	2	2	4	11/13/2007	6.7	4	11/13/2007	Node	2.7	2	2	1	2	2	2	
35	7/27/2007	1	2	1	11/26/2010	44.6	1	No	No	44.6	1	2	2	1	2	2	
36	9/21/2007	2	1	1	9/24/2010	41.1	1	No	No	41.1	1	2	2	1	2	2	
37	3/23/2009	1	2	1	12/23/2010	27.4	1	No	No	27.4	1	2	1	2	2	2	
38	1/7/2010	2	2	1	9/7/2010	12.1	1	No	No	12.1	1	2	1	1	2	2	
39	7/3/2006	2	2	1	11/16/2009	44.5	1	No	No	44.5	1	2	1	1	2	1	
40	10/6/2006	1	2	1	6/9/2007	17.1	1	3/16/2007	Node	14.4	2	2	1	1	2	2	
41	1/16/2010	2	2	4	3/29/2010	6	4	1/21/2010	Node	3.8	1	2	1	2	2	2	
42	9/7/2009	2	2	1	8/3/2010	14.2	5	I/27/2010	Node	8.0	1	2	1	1	2	2	
43	1/19/2010	1	2	2	3/23/2010	6.2	4	3/23/2010	Node	6.2	1	2	1	1	2	2	
44	3/7/2009	1	1	1	1/16/2010	14.7	1	No	No	14.7	1	2	2	2	2	2	
45	3/5/2009	1	2	1	11/17/2010	24.4	1	No	No	24.4	1	2	2	2	2	2	
46	1/8/2010	1	2	1	12/24/2010	16	1	No	No	16.0	1	2	2	2	2	2	
47	3/27/2009	2	2	1	9/28/2010	23.4	1	No	No	23.4	1	2	2	2	2	2	
48	9/11/2006	2	2	1	4/1/2009	35.3	1	No	No	35.3	1	1	1	2	2	2	
49	4/17/2010	1	1	1	10/7/2010	10.1	1	No	No	10.1	1	2	2	2	2	2	
50	2/12/2010	1	2	1	10/21/2010	13.1	1	No	No	13.1	1	2	1	1	2	2	
51	8/22/2006	2	2	1	9/9/2010	52.7	1	No	No	52.7	1	2	1	1	2	2	
52	1/7/2009	2	2	1	8/25/2010	24	1	No	No	24.0	1	2	2	2	2	2	
53	8/22/2007	2	2	1	11/8/2008	18.3	1	No	No	18.3	1	1	2	2	2	2	
54	5/22/2008	2	2	1	11/2/2010	33.4	5	11/2/2010	Node	33.4	1	2	1	2	2	2	
55	6/29/2009	1	2	1	9/15/2010	19.6	1	No	No	19.6	1	2	1	1	2	2	

RCHOP GROUP

S.No	Age	Sex	Date of Dx	Site involved	Bulk	Extranodal	B symp	Performance	HB	CNS	Bone Marrow	LDH	Stage	HANS	IPI	First Cycle	Mid Course
1	61	M	5/12/2006	Cervical	1	2	1	1	13.1	3	NI	440	IIIAX	1	3	5/19/2006	2
2	59	M	6/19/2006	cervical	2	1	1	1	11.7	3	IN	760	IVBE	2	2	7/17/2006	1
3	30	M	8/2/2006	Cervical	2	1	1	2	10.3	3	IN	1974	IVBE	1	3	8/21/2006	1
4	35	M	8/8/2006	Cervical	2	2	1	1	13.4	3	NI	420	IIB	2	1	9/5/2006	1
5	54	M	8/24/2006	Cervical	2	2	2	1	13	3	NI	430	IIIA	1	2	9/24/2006	1
6	37	M	9/26/2006	Cervical	1	2	1	2	13	3	NI	895	IIIBX	2	3	10/16/2006	2
7	32	F	9/12/2006	Inguinal	2	2	2	1	11.1	3	NI	641	IIA	1	1	9/28/2006	1
8	38	F	1/3/2007	Cervical	2	2	2	1	12.1	3	NI	381	IA	2	0	1/15/2007	1
9	58	F	1/24/2007	Cervical	2	2	1	1	12.1	3	NI	405	IIB	2	0	3/3/2007	1
10	64	M	3/19/2007	Cervical	2	2	2	1	12.1	3	NI	418	IIA	2	1	4/3/2007	1
11	30	M	10/30/2007	Cervical	2	2	1	1	10.1	3	NI	420	IIIBS	1	3	11/21/2007	1
12	56	M	4/11/2008	Cervical	2	2	1	1	13	3	NI	614	IIIBS	2	2	4/18/2008	2
13	39	M	7/4/2008	Inguinal	2	2	1	1	14.5	3	NI	359	IIIB	1	1	7/21/2008	1
14	71	F	7/7/2008	Cervical	2	1	2	1	10.4	3	NI	715	IIAE	2	3	7/23/2008	2
15	67	M	12/15/2008	Cervical	2	2	1	2	9.4	3	IN	521	IVB	2	4	1/6/2009	1
16	44	M	1/29/2009	Para-aortic	2	2	2	3	9.4	3	NI	768	IIAE	1	2	2/5/2009	2
17	58	M	1/9/2209	Cervical	2	2	2	1	15.4	3	NI	433	IIA	1	0	1/21/2009	1
18	57	F	3/4/2009	Cervical	2	2	2	1	13.9	3	NI	432	IIA	2	0	3/23/2009	1
19	41	M	2/17/2009	Cervical	2	1	1	1	12.1	2	NI	831	IIIBE	2	3	3/2/2009	2
20	47	M	2/23/2009	Iliac node	1	2	1	2	13	3	IN	647	IVB	1	4	3/13/2009	2
21	54	F	3/13/2009	Cervical	2	2	1	1	9.5	3	NI	789	IIIBS	2	2	3/18/2009	2
22	37	M	5/15/2009	Ingunal	2	2	1	1	14.9	3	NI	3011	IIIB	2	2	5/25/2009	1
23	55	F	8/19/2009	Axillary	2	2	1	1	11	3	IN	1051	IVB	2	2	8/25/2009	1
24	43	M	10/19/2009	Axillary	2	2	1	1	12.5	3	IN	718	IVB	2	2	11/2/2009	2
25	60	F	10/20/2009	Inguinal	2	2	1	3	12.6	3	IN	1612	IVB	1	4	11/2/2009	2

S.No	Date of Compleltion	CNS therapy	Radiot herapy	Status post six cycle	Date LFU	Months	Stat us LFU	Relapse	Month CR	Alive	Lost to follow	Neu trop enia	Hyp ergl yce mia	Neu ropa thy	SIADH	Others
1	9/14/2006	2	1	1	2/25/2008	21.5	1	No	21.5	2	1	1	1	2	2	
2	11/3/2006	2	2	1	11/20/2007	17.1	5	2/23/2007	8.2	2	2	1	2	2	2	
3	12/6/2006	2	2	1	7/9/2010	47.2	5	7/13/2007	11.3	1	2	1	2	1	2	
4	12/21/2006	2	2	1	9/26/2008	25.6	1	No	25.6	2	1	2	2	2	2	
5	1/8/2007	2	2	1	11/22/2010	51	1	No	51	1	2	2	1	2	2	
6	1/27/2007	2	2	1	8/5/2010	46.3	1	No	46.3	1	2	1	2	2	2	
7	1/21/2007	2	2	1	6/15/2009	33.1	1	No	33.1	1	2	2	2	2	2	
8	5/7/2007	2	2	1	8/28/2009	31.8	1	No	31.8	1	2	2	2	2	2	
9	6/20/2006	2	2	1	7/7/2008	17.4	5	12/19/2007	10.8	2	2	1	2	2	2	
10	7/27/2007	2	2	1	3/28/2008	12.3	5	2/20/2008	11.1	2	2	1	2	2	2	
11	4/18/2008	2	2	1	11/4/2008	12.2	1	No	12.2	2	2	2	2	2	2	
12	9/23/2008	2	2	1	8/20/2010	28.3	1	No	28.3	1	2	1	2	2	4	
13	11/4/2008	2	2	1	12/9/2010	29.2	1	No	29.2	1	2	1	2	2	2	
14	11/23/2008	2	2	1	1/27/2009	6.7	1	No	6.7	1	2	2	1	2	2	
15	7/3/2009	2	2	1	7/9/2010	18.8	1	No	18.8	1	2	1	1	2	2	
16	5/21/2009	2	1	1	11/27/2010	24	1	No	24	1	2	1	2	2	2	
17	5/19/2009	2	2	1	12/28/2010	23.6	1	No	23.6	1	2	2	2	2	2	
18	7/10/2009	2	2	1	1/22/2010	10	1	No	10	1	2	2	2	2	2	
19	7/16/2009	1	1	1	10/21/2010	20.1	1	No	20.1	1	2	1	2	1	2	
20	6/26/2009	2	2	2	9/22/2010	18.9	3	No	18.9	1	2	1	2	2	2	DVT
21	6/30/2009	2	2	1	8/3/2010	16.7	1	No	16.7	1	2	2	2	2	2	
22	9/15/2009	2	2	1	12/24/2010	19.3	1	No	19.3	1	2	2	2	2	2	
23	12/8/2009	2	2	1	9/14/2010	12.8	1	No	12.8	1	2	1	2	2	2	
24	5/12/2010	2	1	1	9/24/2010	11.2	1	No	11.2	1	2	1	2	2	2	
25	1/29/2010	2	2	4	5/19/2010	6.9	4	1/29/2010	4	1	2	1	2	2	2	DVT

S.No	Age	Sex	Date of Dx	Site involved	Bulk	Extranodal	B symp	Performance	HB	CNS	Bone Marrow	LDH	Stage	HANS	IPI	First Cycle	Mid Course
26	53	M	12/9/2009	Cervical	2	1	2	1	10.7	2	IN	415	IVAE	2	2	12/9/2009	1
27	60	F	12/14/2009	Cervical	1	1	2	1	10.6	3	NI	2614	IIAXE	2	2	22/12/2009	2
28	52	M	3/19/2010	Axillary	2	2	1	1	13.1	3	NI	339	IIIB	1	1	3/25/2010	2
29	54	F	10/6/2009	Cervical	2	2	1	2	9	3	IN	662	IIB	2	2	10/19/2009	1
30	22	M	2/18/2009	Cervical	2	1	1	2	12	3	IN	978	IVBE	1	3	2/28/2009	1
31	53	M	3/9/2007	Inguinal	2	2	2	1	7.2	3	IN	683	IVAE	2	3	3/19/2007	1
32	43	M	10/9/2007	cervical	2	1	2	1	13.1	3	NI	766	IIAE	2	2	10/10/2007	1
33	34	M	2/20/2008	Axillary	2	2	1	1	10.3	3	NI	489	IB	2	1	2/27/2008	1
34	48	M	9/5/2007	cervical	2	2	1	1	10.9	2	NI	1080	IIIBS	2	2	9/16/2007	1
35	53	M	3/13/2010	Mediastinal	2	1	2	2	14.9	3	NI	2885	IIIAE	2	4	3/23/2010	1
36	37	F	4/31/2007	Para-aortic	2	2	1	1	9.4	3	NI	749	IIIBS	1	2	5/1/2007	1
37	36	M	3/31/2010	Inguinal	1	2	1	1	11.7	3	IN	780	IVB	2	3	4/15/2010	1
38	69	F	11/22/2007	Mesentric mass	2	2	1	2	14.1	3	NI	473	IIIAS	1	4	30/11/2007	2
39	45	F	1/7/2010	Cervical	2	2	2	1	12.2	3	NI	483	IA	1	1	1/23/2010	1
40	42	F	1/25/2010	Retroperitonium	1	1	1	1	9.4	3	NI	1339	IIIBEX	2	3	2/10/2010	2
41	62	M	1/3/2008	Vertbra	2	1	2	2	13.1	2	NI	826	IVAES	2	4	1/14/2008	2
42	64	F	7/28/2006	Axilla	2	1	1	1	6.7	2	NI	787	IIIBE	2	4	8/15/2006	1
43	61	M	7/4/2007	Abdomen	2	2	1	1	15.2	3	NI	703	IIB	1	2	7/10/2007	2
44	72	M	6/11/2009	Cervical	2	2	1	2	14.1	3	NI	582	IIB	1	2	6/18/2009	1
45	20	M	1/27/2009	Cervical	2	2	2	0	14.7	3	NI	487	IIA	2	0	2/5/2009	1
46	56	M	1/23/2010	Cervical	1	2	1	2	13.6	3	NI	2457	IIIBX	1	3	2/1/2010	2
47	63	M	12/5/2008	Tonsil	2	1	2	1	13.7	2	NI	800	IIIAE	1	3	1/6/2009	1
48	29	M	11/16/2007	Tonsil	2	1	2	1	17.2	3	NI	414	IAE	1	0	11/19/2007	1
49	26	F	10/5/2007	Nasophyx	2	1	2	1	12.7	2	NI	552	IIAE	1	1	10/10/2007	2
50	76	M	1/3/2007	Retroperitonium	1	2	1	2	12.4	3	NI	959	IIBX	1	2	1/11/2007	2
51	51	M	5/30/2009	Cervical	2	2	1	3	8.7	3	NI	388	IB	1	0	6/3/2009	1

S.No	Date of Compleltion	CNS therapy	Radiot herapy	Status post six cycle	Date LFU	Months	Stat us LFU	Relapse	Month CR	Alive	Lost to follow	Neu trop enia	Hyp ergl yce mia	Neu ropa thy	SIADH	Others
26	3/26/2010	1	2	1	10/8/2010	10	1	No	10	1	2	2	1	2	2	2
27	4/13/2010	2	2	4	6/18/2010	6.1	4	5/18/2010	5.1	1	2	2	21	2	2	2
28	7/13/2010	2	2	3	11/9/2010	7.7	3	No	7.7	1	2	2	1	2	2	2
29	2/12/2010	2	2	1	9/3/2010	10.9	1	No	10.9	1	2	2	1	1	2	2
30	7/3/2009	2	2	1	5/28/2010	15.2	1	No	15.2	1	2	2	1	2	2	2
31	8/27/2007	2	2	1	6/15/2009	27.2	1	No	27.2	1	2	2	2	1	2	2
32	2/12/2008	1	2	1	7/26/2010	33.5	1	No	33.5	1	2	2	1	2	2	2
33	6/10/2008	2	2	1	10/1/2010	31.3	1	No	31.3	1	2	2	2	2	2	2
34	1/4/2008	2	2	1	11/24/2008	14.7	5	5/10/2008	8.1	2	1	2	1	2	2	2
35	7/6/2010	2	2	1	11/9/2010	7.9	1	No	7.9	1	2	2	1	2	2	2
36	8/17/2007	2	2	1	6/8/2008	13.3	5	11/27/2007	6.9	2	1	2	1	2	2	2
37	7/30/2010	2	1	1	12/3/2010	8.1	1	No	8.1	1	2	2	2	2	2	2
38	4/23/2008	2	2	1	12/23/2010	37	5	1/25/2010	26.1	1	2	2	1	2	2	2
39	8/5/2010	2	2	1	12/3/2010	10.8	1	No	10.8	1	2	2	2	2	2	2
40	5/28/2010	2	2	3	10/7/2010	8.4	3	No	8.4	1	2	2	1	2	2	2
41	4/9/2008	2	1	1	10/26/2010	33.7	5	9/15/2009	20.4	1	2	2	1	1	2	2
42	12/1/2006	2	2	1	7/22/2008	28.7	5	12/31/2007	22	2	1	2	1	1	1	1
43	11/7/2007	2	2	3	3/15/2008	8.4	5	12/6/2007	5.1	2	1	2	1	1	2	2
44	9/29/2010	2	2	1	11/23/2010	17.4	1	No	17.4	1	2	2	1	1	2	1
45	6/3/2009	2	2	1	8/27/2010	19	1	No	19	1	2	2	2	2	2	2
46	6/12/2010	2	2	1	9/24/2010	8	1	No	8	1	2	2	1	1	2	2
47	5/6/2009	1	2	1	9/15/2009	9.3	1	No	9.3	1	2	2	1	1	2	1
48	3/19/2008	2	2	1	9/14/2010	33.9	1	No	33.9	1	2	2	2	2	2	2
49	2/13/2008	1	1	1	3/23/2010	29.6	1	No	29.6	1	2	2	1	2	2	2
50	5/4/2007	2	2	1	4/21/2009	27.6	1	No	27.6	1	2	2	1	1	2	2
51	10/22/2009	2	2	1	10/14/2010	16.5	1	No	16.6	1	2	2	1	1	2	1