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Original Article

Clinical profile and survival outcomes of Non-Hodgkin B-cell Lymphoma: Retrospective Study from a tertiary care centre in Southern India

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ABSTRACT

Background: Non-Hodgkin lymphomas (NHL) represent a group of lymphoproliferative disorders originating from either B or T lymphocytes, with a limited understanding of their clinical spectrum particularly in developing countries(1). Combining the anti-CD20 monoclonal antibody rituximab with chemotherapy is the gold standard for frontline treatment (2). **Methods**: A retrospective review of non-Hodgkin B-cell lymphoma cases diagnosed and treated at tertiary centre in Southern Kerala, India between January 2011 and December 2019 was done. The aim of this study was to evaluate the clinicopathological features and survival rates of non-Hodgkin B-cell lymphoma patients during the study period. **Results**: A total of 190 B-cell NHL patients were included, with a median age of 57 years (Interquartile range 49-64years), showing a higher frequency among males (63.2%). Peripheral lymphadenopathy was present in 89.4% (170) patients, organomegaly in 11.1% and extranodal involvement in 13.7% patients. Staging at diagnosis revealed a predominance of stage 3 disease (51.6%). Diffuse large B-cell lymphoma (DLBCL) was the most common biopsy type (51.1%). All patients received the first line chemotherapy with CHOP regimen with or without Rituximab based on CD 20 positivity. Radiotherapy was performed in 40 (18%) patients. Post treatment reassessment showed complete response in 76.7% (102) patients. The survival probability at one year was 87%, decreasing slightly to 85% at 2 years and further declining to 80% at 5 years.
Conclusion: The retrospective review showed that our patient population outcomes of non hodgkins lymphoma are comparable to results from developing countries. These findings highlight the diverse clinical characteristics of NHL patients and underscore the need for tailored therapeutic strategies.

Keywords: *Non-Hodgkin lymphoma, retrospective study on lymphoma.*

INTRODUCTION

Lymphomas represent a diverse array of malignancies that arise from the clonal proliferation of B- cell, T- cell and natural killer (NK) cell subsets of lymphocytes at different stages of maturation(3). Lymphoma is broadly classified into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL), the latter accounts for more than 85% of cases (3). The pathogenesis of NHL is believed to be multifactorial, including infectious, or environmental exposure (e.g., chemical), immunodeficiencies (e.g., AIDS), autoimmune disease, and genetic aberrations (4). There is currently limited published data that can guide patient selection for this treatment regarding both toxicities and outcomes (5). The international prognostic index (IPI) and the age-adjusted IPI (aaIPI) are two indexes used to identify DLCBL patients with a higher probability of survival (6). Four discrete outcome groups were identified with a 5-year overall survival ranging from 32% to 83% (7). CHOP regimen is the standard treatment used for NHL since the 1970s, with only 30–40% overall survival (8). Subsequent new combinations including drugs, such as methotrexate, bleomycin or cytarabine have been employed, however, multicentre randomized trials failed to demonstrate any survival advantage of these second and third generation regimens over standard CHOP. The addition of rituximab to chemotherapy regimens has significantly improved outcomes

in non-Hodgkin lymphoma especially DLBCL (9). However, its widespread use in developing countries is still limited by the lack of financial coverage (10). This study was conducted to evaluate the clinicopathologic profile, treatment outcomes and prognosis of non hodgkins lymphoma in a tertiary care centre in a developing country.

MATERIALS AND METHODS

A retrospective chart review of non-Hodgkin lymphoma patients diagnosed and treated during the period January 2011 to December 2019 in a tertiary centre was done. This study was registered and the approval for this study was obtained from the Institutional Ethics Committee. Patient profiles, including presenting symptoms, laboratory and histopathology results, staging and treatment plans, and their outcomes were reviewed from patient's medical records. The diagnosis of NHL was confirmed through histological examination of a lymph node biopsy/tissue and immunohistochemical stains, following the World Health Organization (WHO) classification (11). Patients were staged according to the Ann Arbor Staging system after clinical examination, contrast-enhanced computed tomography (CECT) or positron emission tomography (PET-CT), and a bone marrow examination if warranted (12). Patients received 6–8 cycles of CHOP chemotherapy (Cyclophosphamide, Doxorubicin hydrochloride, Vincristine sulfate, and prednisone) based on Ann Arbor staging, with or without adding Rituximab based on CD 20 positivity (13). This was followed by involved site radiotherapy if the disease was initially bulky or reassessment PETCT showed residual lesion with metabolic activity (14). Patients with refractory or relapsed disease were administered salvage chemotherapy, followed by referral for high dose chemotherapy and autologous stem cell transplantation, whenever feasible (15). Treatment responses were defined as complete response, partial response, progressive disease and stable disease after imaging which included CECT or PET-CT. Overall survival (OS) was calculated from the date of diagnosis to the date of death or last follow-up. Progression-free survival (PFS) was calculated from the date of diagnosis until the date of progression or death or follow-up. Statistical analysis of data was done using the R statistical software. Categorical data were expressed as frequencies with percentages and continuous data were expressed as mean and standard deviation. Survival was estimated by the Kaplan-Meier method. Potential prognostic factors like age, gender, B-symptoms, clinical stage, presence of extranodal sites, organomegaly, histopathology evaluation, treatment regimens, haemoglobin, erythrocyte sedimentation rate (ESR), serum lactate dehydrogenase level, age adjusted international prognostic score, treatment response outcomes were analysed for OS and PFS by applying the two-sided log-rank test. Cox proportional hazards model was used for bivariate analysis to evaluate potential factors associated with OS and DFS. All P-values were two sided and P-values <0.05 were considered statistically significant.
(The baseline characteristics analysed in the study are depicted in Table No 1).

Table 1 showing the baseline characteristics of patients

Baseline characteristics		Number (%)
Age	<60 >60	114(60) 76(40)
Sex	Females Males	70(36.8) 120(63.2)
B symptoms	Yes No	6(3.2) 184(96.8)
Lymphnodes	cervical abdominal others	48(26.4) 15(8.2) 27(14.8)
Performance status	yes no	188(99.5) 1(0.5)
Organomegaly	yes no	21(11.1) 169(88.9)
Bone marrow	positive negative	7(3.8) 177(96.2)
Stage	Favourable Unfavourable	55(29.3) 133(70.7)
Biopsy	DLBCL Follicular	97(51.1) 50(26.3)
Chemotherapy	RCHOP CHOP	67(40.9) 72(43.9)
Extranodal involvement	yes No	26(13.7) 164(86.3)
IHC	CD20+ CD20-	135(71.1) 55(28.9)
Stages	I II III IV	17(8.9) 56(29.5) 98(51.6) 19(10)
aaIPI	Low	8(4.2)

	Intermediate High	78(41.1) 104(54.7)
RT	Yes No	18(40) 27(60)
Treatment response	CR PR PD	102(76.7) 28(21.1) 2(1.5)
Status at last follow-up	Dead Lost follow-up Alive with disease Alive without disease	25(13.2) 35(18.4) 30(15.8) 100(52.6)

RESULTS

Our cohort included 190 patients, with a median age of 57 years (interquartile range 49 to 64.75 years). The study showed a male predominance (63.2%) and 40% (76) of patients were aged more than 60 years old. Peripheral lymphadenopathy was present in 89.4% (170) patients with B symptoms reported in 3.2% patients. Most of the patients (99.5%) belong to ECOG performance status 1. Hepatosplenomegaly was noted in 11.1% of patients, while extranodal involvement was present in 13.7% patients (eye, nasal cavity, nasopharynx, breast, gastrointestinal tract, spleen, testis, bone). Bone marrow positivity was detected in 3.7% of the cohort. Staging at diagnosis revealed a predominance of stage 3 disease (51.6%), followed by stage 2 (29.5%), stage 4 (10%), and stage 1 (8.9%). 29.3% (55) patients belong to favourable group. Age-adjusted international prognostic score was low in 4.2% (8), intermediate in 41.1% (78) and high in 54.7% (104) patients. Diffuse large B-cell lymphoma (DLBCL) was the most common biopsy type, observed in 51.1% (97) followed by follicular lymphoma 26.3% (50) of patients. Other biopsy subtypes include Tcell, peripheral T cell, lymphoblastic, mantle cell, Burkitt lymphoma. CD20 positivity was identified in 71.1% of the cases. All patients received the first line chemotherapy with CHOP regimen with or without Rituximab based on CD 20 positivity. Radiotherapy was given to 18% (40) patients. Treatment response after reassessment showed complete response in 76.7% (102), partial response in 21.1% (28). The disease was relapsed in 14.2% (27) patients, 88% of them had second line chemotherapy regimens such as Rituximab Bendamustine, Rituximab Ifosfamide,Carboplatin and Etoposide, MINE, Rituximab Chlorambucil). 38.9% (74) patients had Hemoglobin less than 12, 32.6% (62) patients had raised erythrocyte sedimentation rate and 87.3% (166) patients had raised Lactate dehydrogenase. On survival analysis the median disease-free survival time was not reached and at the last follow-up, the 5-year survival probability was 63.4%. The mean OS was calculated to be 87.6 months (95% CI: 81.05 - 94.06). At 12 months, the survival probability was 87%, decreasing slightly to 85% at 24 months and further declining to 80% at 60 months. In the univariate analysis, several prognostic factors such as age, gender, performance status, extranodal status, age adjusted IPI, raised LDH were analysed for any associations with the survival and our study showed performance status , gender and age adjusted IPI had influenced survival rates.

DISCUSSION

Management of patients with NHL has changed substantially over the past two decades with improved diagnostic techniques, newer treatment options, and consequently better treatment outcomes. Understanding the biology has contributed to a significant impact in the treatment and prognosis (16). Non-Hodgkin lymphoma comprises 2.8% of worldwide cancer diagnoses. The global age standardized risk of NHL was 6.7 among men and 4.7 among women, translating to a 0.72% and 0.35% cumulative lifetime risk for men and women, respectively (17). The average age of diagnosis was 67, with 57% of diagnoses made in those >65 years old. Our cohort reported median age of 57 years 40% of patients more than 60 years old and 63.2% were males (63.2%).

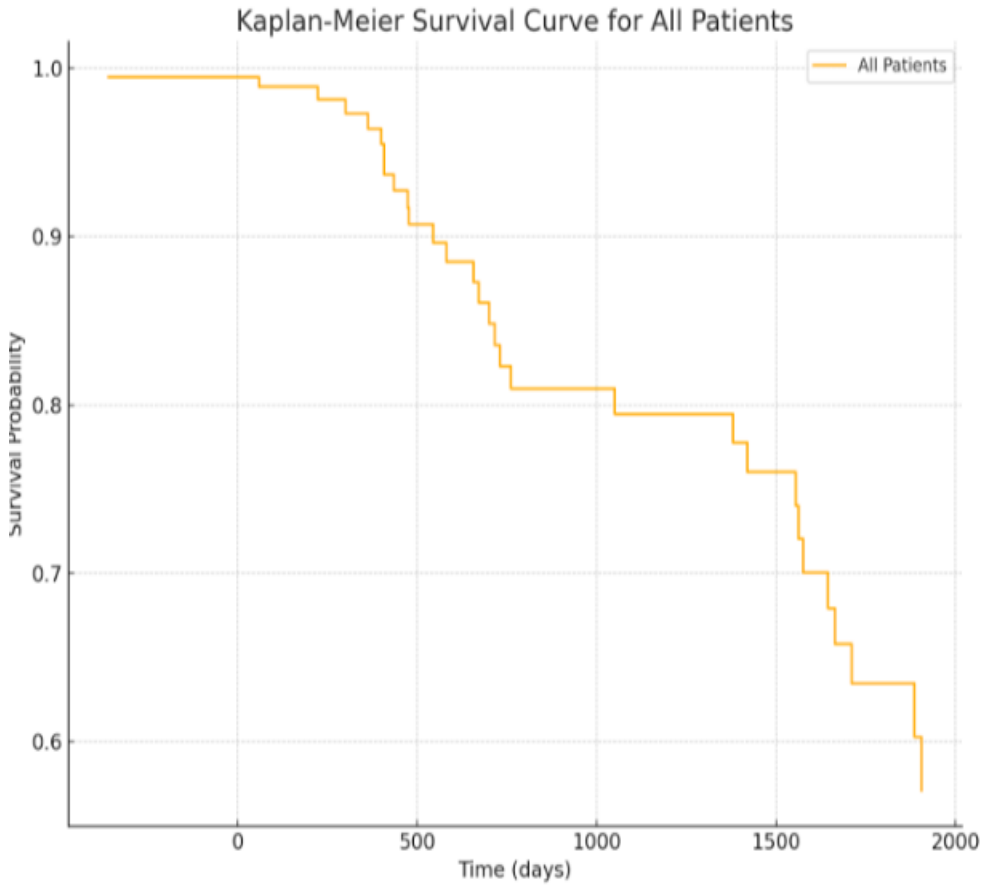
Diffuse large B-cell lymphoma was the most common type (51.1%), and 89.4% of patients presented with peripheral lymphadenopathy. Majority (70.6%) presented with an advanced stage of disease. A similar pattern was observed in literature especially from developing countries (18)(7)(19). In NHL especially DLBCL early stage, tumor bulkiness and stage adjusted international prognostic index are the main determinants of prognosis and treatment (20). Extra nodal sites and bulk of the tumor are significant predictors and prognostic factors for treatment outcome too. The age adjusted international prognostic index (aa-IPI) takes into account factors that are mostly linked to the patient characteristics, for patients aged more or less than 60 years, lactate dehydrogenase level, performance status and clinical stage (Early versus Advanced). These components might act as prognostic markers for non-Hodgkin lymphoma (7). Compared to patients with nodal disease, studies reported conflicting outcomes on associating increased relapse with extranodal disease. Our study showed no difference in survival with extranodal disease or tumor bulkiness but showed a trend of significant association with age adjusted international prognostic index, which is similar to the data from developing countries (21). The loss of CD20 expression is associated with extranodal involvement, a more aggressive clinical course, loss of responsiveness to rituximab and conventional chemotherapy, leading to poor prognosis. Novel agents targeting B-cell signalling pathways, monoclonal antibodies, checkpoint inhibitors, might pave way in the therapy of CD 20 negative B-cell lymphomas (22). The positive impact of radiotherapy on survival outcomes in patient was also reported in other studies (20) (23). RT has diverse utility in the definitive, consolidative, salvage and palliative settings, either alone or in combination with multi-agent chemoimmunotherapy. Even after statistical adjustments, patients who received systemic therapy alone had significantly inferior OS compared to those who received both (23). Elevation of LDH is a valuable biomarker and is

associated with a higher tumor burden and more aggressive behavior of NHL, as well as an increased risk of central nervous system (CNS) relapse(7). Likewise raised ESR and anemia has got a prognostic significance in non-Hodgkin lymphoma outcome (24).

In our study complete response is seen in 76.7% patients after first line chemotherapy and 13.7% patients relapsed over the period of the study. Complete remission can be achieved in 60-80 % of diffuse aggressive non-Hodgkin lymphomas. However 20-40% of them will eventually relapse (25). It is reported to have a significant correlation between response rate and median PFS in NHL. Objective response rate was as good as CR rate in predicting median PFS. So these determined quantitative relationships can be used to project the median PFS based on ORR or CR, enabling better decision making in the development of new NHL therapies(26)(27). Lower complete response rates and higher relapse rates contributed to an increased risk of death. Furthermore, patients with poor performance status were found to have a higher treatment-related death rate (28).

The Kaplan–Meier curve for disease free survival showed a steady decline over time, especially in the initial years following diagnosis. . The 5-year disease free survival probability was 63.4%. The median disease-free survival time was not reached during the study period, as more than 50% of the patients remained disease free by the end of the study. This highlights the importance of continuous monitoring and intervention to reduce long-term risk. Routine follow-up visits should be frequent during the first 2-3 years after completion of treatment. History and physical examination are efficient and cost-effective tools for relapse detection (25). (Kaplan–Meier curve for disease free survival is depicted in figure no. 1)

Figure 2 showing the Kaplan–Meier curve of disease free survival of patients



The Kaplan-Meier survival curve for evaluating the overall survival (OS) also spans over a follow-up period of 100 months. The median OS was not reached during the study period, the mean OS was calculated to be 87.6 months (95% CI: 81.05 - 94.06). At 1 year, the survival probability was 87%, decreasing slightly to 85% at 2 year and further declining to 80% at 5 year. The survival curve exhibited an initial steep decline during the first 12 months. The restricted mean survival time (RMST) analysis at 100 months was 83.5 months (95% CI: 77.42 - 89.59 months). The RMST curve, depicted with shaded areas representing 95% confidence intervals, highlights the variability in survival across the follow-up period. As per SEER data overall survival at 5years for stage II is 74% and all stages combined is 65% (29)(3)(30). The overall survival (OS) across different risk groups stratified by the age adjusted International Prognostic Index (aaIPI) was done. aaIPI Low Risk consisted of 8 patients, with a mean survival of 84.0 months (95% CI: 62.60 - 105.39 months). aaIPI Intermediate Risk comprised of 78 patients had a mean survival of 89.0 months (95% CI: 78.47 - 99.53 months). aaIPI High Risk included 104 patients, had a mean survival of 78.5 months (95% CI: 71.18 - 85.79 months). This shows that the low-risk group has

the most favorable prognosis and the high-risk group the least favorable. However, the log-rank test showed that the difference was not statistically significant (P = 0.7614). The RMST was 83.0 months (95% CI: 61.90 - 104.19) for aaIPI lowrisk, 80.7 months (95% CI: 71.65 - 89.72) for aaIPI intermediate risk, and 78.5 months (95% CI: 71.18 - 85.79) for aaIPI high risk. Pairwise comparisons of RMST between the groups did not reveal significant differences. Though the lack of statistical significance suggests that differences in survival between the groups may not be as pronounced in this cohort. Several trials have published data regarding the prognostic impact of the aaIPI with multivariate analysis showing that only aaIPI retained its significance as an independent predictor of outcome (31) (6). (Kaplan–Meier curve for overall survival is depicted in Figure No 2)(Kaplan–Meier curve for overall survival adjusted for aaIPI is depicted in Figure No. 3)

Cox Proportional Hazards Regression Analysis included aaIPI, ECOG performance status, disease grade, and gender, but only the ECOG performance status was identified as the most significant predictor of overall survival (OS). aaIPI (HR = 1.20, 95% CI: 0.58 - 2.49, P = 0.626), disease grade (HR = 1.13, 95% CI: 0.59 - 2.18, P = 0.712), gender (HR = 0.53, 95% CI: 0.24 - 1.19, P = 0.126) were found to be not significantly associated with survival outcomes in this cohort. Future research should explore additional factors that may predict or prognosticate the survival in NHL both genetic and molecular markers, along with clinical indicators.

Figure 1 showing the Kaplan–Meier curve of overall survival of patients

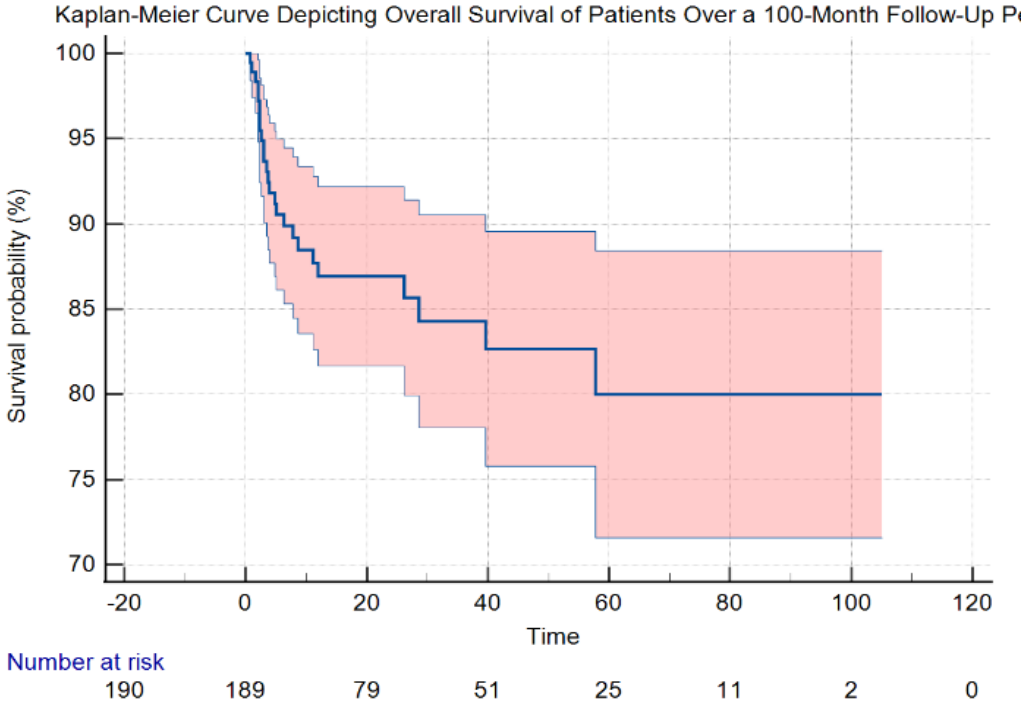
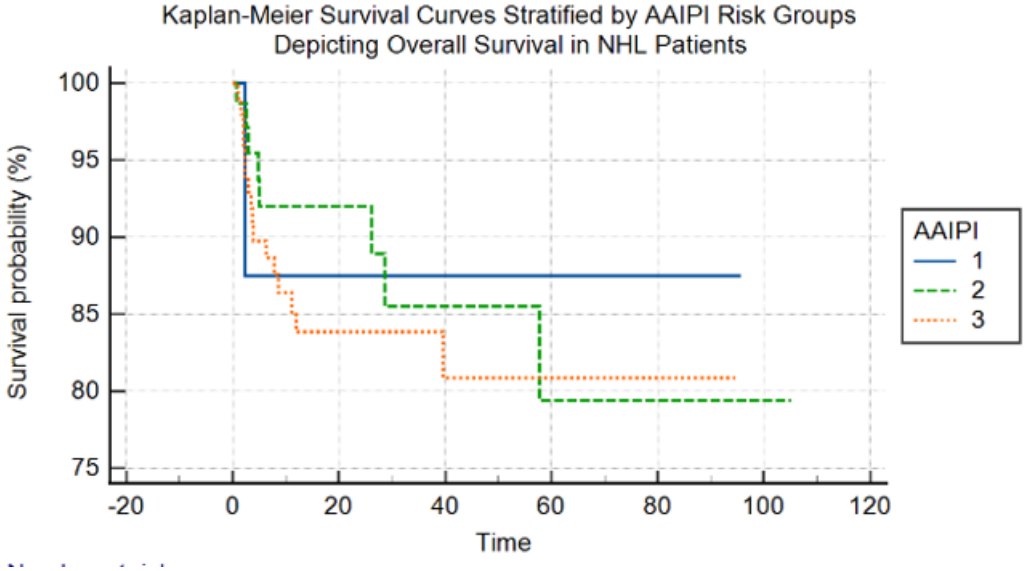


Figure No 3 showing overall survival curves stratified by aaIPI risk groups



As for limitations, this study is a single institution tertiary care centre, retrospective cohort study with a short follow-up time. The study population is small yet encompassing different subtypes of non-Hodgkin B-cell lymphoma, making it difficult to analyze relevant treatment prognostic factors and subtype survival outcomes. A longer follow-up is needed to explore differences in various subtypes and in outcomes with various chemotherapeutic regimens. Multi-center longitudinal studies should be done in the future for a better understanding of the clinical and therapeutic profile of non-Hodgkin lymphoma.

CONCLUSION

The etiology and prognosis of NHL remain scarcely understood hence optimised diagnosis and management in non-Hodgkin's lymphoma is challenging. This retrospective analysis of non-Hodgkin Lymphoma patients from a tertiary cancer centre showed that out of 190 patients, 76.7% showed complete response rates, 13.7% patients had relapsed with 5 year survival rates at 80% with performance status, gender and age adjusted IPI predicting an association on their survival. The patient population outcomes are comparable to clinical reports from developing countries but multicenter studies are needed to further explore the possibilities of different chemotherapy regimens and improvement in clinical outcomes.

ABBREVIATIONS

- NHL: Non-Hodgkin Lymphoma
- CECT: Contrast-enhanced computed tomography
- PET-CT: Positron emission tomography
- CR: Complete Response
- OS: Overall survival
- PFS: Progression-free survival
- Hb: Hemoglobin
- ESR: Erythrocyte sedimentation rate
- LDH: Lactate dehydrogenase
- aaIPI: Age-adjusted International prognostic score
- RCHOP: Rituximab, Cyclophosphamide, Doxorubicin hydrochloride, Vincristine sulfate, and prednisone
- RCVP: Rituximab, Cyclophosphamide, Vincristine sulfate, and Prednisone.
- MINE: Mesna, Ifosfamide, Mitoxantrone, Etoposide
- COP: Cyclophosphamide, Vincristine, Prednisone
- RICE: Ifosfamide, Carboplatin, and Etoposide.

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