DLBCL First Line Treatment

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The aggressive non-Hodgkin's lymphomas can be cured in more than half of the cases. For patients with localized aggressive non-Hodgkin's lymphoma, heterogeneity in patients selection prevent us from defining a new standard of care. On the contrary, for patients with advanced stages of diffuse large B cell lymphoma a new standard of therapy now exist particularly for elderly and low risk young patients.

In this article I will separate the patients into 3 different groups: I) early stage NHL, II) advanced stage elderly and low risk young patients and III) young high risk patients.

I. Early (Limited) Stage Aggressive Lymphoma

There is extreme heterogeneity within the group of patients described as having early stage lymphoma, making comparisons of outcome difficult.

SWOG compared 3 cycles of CHOP with RT to 8 cycles of CHOP in patients with localized aggressive NHL and found that CHOP(3) plus RT was superior to CHOP (8) through the first five years of follow-up (1) . Localized disease was defined as stage I and non-bulky stage II disease. Patients with bulky-stage II disease are known to have a prognosis similar to patients with advanced disease and should be excluded from limited-stage disease (2). Patients with bulky-stage II disease accrued to SWOG studies had a 5-year survival of 49%. Patients with stage III-IV disease had a 5-year survival of 46%. Therefore bulky stage II is considered as "advanced" disease. If patients with bulky-stage II disease are included in trials and treated with a short-course of chemotherapy plus RT they have an inferior outcome compared to similar patients treated with aggressive chemotherapy designed for advanced disease.

Reyes and colleagues from GELA (3) have reported the results of a randomized trial comparing CHOP (3) plus RT to an aggressive combination chemotherapy called ACVBP (LNH-93-1). ACVBP chemotherapy was originally designed for advanced disease. In the subgroup of bulky-stage II disease, treatment with ACVBP was superior to CHOP(3) plus RT with 5-year survival estimates of 82% and 50%, respectively (p=0.03)

By excluding patients with bulky-stage II disease one might presume that the remaining patients with limited disease comprise a homogeneous group with regard to prognosis and choice of optimal therapy. But 10 year survival can vary from 90% to 10% within subgroup of limited stage patients (4). Predicting such variable outcome easily accomplished using stage modified IPI. Most clinicians uses IPI and it includes five risk factors including age, stage, serum LDH, performance status(PS), and the number of extranodal sites of disease(5). Age, stage, serum LDH, and PS each predict significant outcome differences for patients with limited diseases. Patients with no adverse risk factors have a very good prognosis with 10 year survival estimates exceed 90% treated (Table 1 and 2). These very good results can be achieved regardless of the treatment strategy chosen; CHOP (3) +RT, CHOP (8), or ACVBP (1,4,6). This category is called 'very limited disease'.

Another GELA study was published by Fillet et al. comparing 4 cycles of CHOP to CHOP plus 40 Gy involved-field RT in patients older than 60 years with no adverse risk factors according to the age-adjusted IPI (7). There was no advantage of the radiation and, a possible disadvantage in patients older than 70 years of age. Recent ECOG study suggested benefit of adjuvant radiation after 8 cycles of CHOP (8). But the main difference in these two trials was bulky disease rates. Although SWOG included only 6 (1.5%) bulky (stage I) patients, the rate of bulky disease in ECOG was 31%. So one third of the patients actually should be accepted as advanced disease in ECOG trial.

The MINT trial included some patients with early stage disease and compared a CHOP-like chemotherapy regimen to the same regimen with the addition of rituximab in young, good prognosis patients (9). For the most favorable patients (those without bulky disease) the results with a complete course of chemotherapy plus rituximab alone without radiation led to survival in excess of 90%. The Southwest Oncology Group in the United States reported a pilot study of an abbreviated course of CHOP plus rituximab followed by radiation showing progression free and overall survival in excess of 90% (10)

II. Treatment Of Advanced Stage Elderly And Low Risk Young Patients

After initial staging bulky stage II, stage III or stage IV aggressive lymphoma is documented in approximately 75% of all DLBCL patients. Therefore chemotherapy is main treatment modality for these patients.

The study that defined chemotherapy as standard was an intergroup trial conducted by SWOG and ECOG. In this study previously untreated patients with stage II bulky, III, and IV disease with intermediate –or high-grade histology were randomized to one of four treatment arms: CHOP, m-BACOD,, ProMACE-CytaBOM or MACOP-B. There was no difference in any treatment arm. These results along with the fact that CHOP was cheaper and easier to administer than the other regimens, established CHOP as the standard therapy throughout the world. However, with a projected disease-free survival rate of 36%, it is obvious that it is far from an ideal therapy, and there is need for better treatment approaches.(11)

The International non-Hodgkin Lymphoma Prognostic Factors Index (IPI) utilized pretreatment prognostic factors in a sample of over 5000 patients to develop a predictive model of outcome for aggressive non-Hodgkin's Lymphoma (12). Five pretreatment characteristics were found to be independent predictors of death: age (< 60 vs. >60), tumor stage II or II vs. III or IV, the number of involved extranodal sites (< 1 vs. >1), patient ECOG performance status (0,1;ambulatory vs. >2 ;non-ambulatory), and serum LDH level(normal or elevated). Each of the individual factors had comparable relative risks. The resulting model identified 4 risk groups with the following associated 5- year survival rates: low risk(0-1), 73%, low-intermediate risk (2 risk factors), 51% ; high- intermediate risk (3 risk factors), 43%, and high risk (4-5 risk factors), 26%. However, the improvement in treatment response associated with the addition of the antibody rituximab to treatment regimens seems to have altered survival of prognostic groups using the International Prognostic Index (13). (Table 3)

Table 1. International Prognostic Index (12)

Full Index		Age Adjusted	
Prognostic Factors Age> 60 years Performance status > 2 LDH> 1 x normal Extranodal sites >2 Stage III or IV		Prognostic Factors • Performance status > 1 • LDH > 1 x normal • Stage III or IV	
Risk Category	Factors	Risk Category	Factors
• Low	0 or 1	• Low	0
• Low-intermediate	2	• Low-intermediate	1
• High-intermediate	3	• High-intermediate	2
• High	4 or 5	• High	3

Table 2. Outcome for patients with diffuse aggressive lymphoma after anthracycline chemotherapy International Index (12)

Risk Category	No Risk Factors	% Cases	CR rate	PFS of CRs 5 yr	Survival 5 yr
Low	0,1	35%	87%	70%	72%
Low-intermediate	2	27%	67%	50%	50%
High-intermediate	2	22%	55%	48%	43%
High	4,5	16%	44%	40%	26%

Table 3. Results with a revised IPI when R-CHOP is given for diffuse large B-cell lymphoma (13)

Group	No Factors	% Patients	% 4-Year Overall Survival
Standard IPI	0,1	28	86
	2	27	81
	3	21	54
	4,5	24	58
Revised IPI	0	10	92
	1,2	45	82
	3,4,5	45	58

Currently molecular profiling project has used complementary DNA (cDNA) microarray techniques to demonstrate two distinct subpopulations

of DLBCL with different prognosis and different genetics. Patients with a germinal center B (GCB) cell like signature have a more favorable course than those with an activated B-cell (ABC) signature (14,15). At the present time gene expression profiling is not part of routine clinical practice (37). This may be due to technical difficulties in performing the c-DNA arrays. GCB versus ABC typing seems to be able to be reproduced by tissue microarray (16).

After the disappointing results with the third generation chemotherapy regimens, several new treatment approaches have been developed. GELA developed the ACVBP regimen (which involves very intensive chemotherapy for four courses followed by an intensive consolidation) which was shown to be superior to CHOP in subgroup of patients (17).

German high-grade lymphoma study group found that addition of etoposide to CHOP improved results in young patients (18), while CHOP administered at 14 day instead of 21 day intervals seemed to improve the results in elderly patients (19).

An infusional chemotherapy regimen developed at the National Cancer Institute referred to as DA-EPOCH had very encouraging results (20).

The randomized study that changed practice throughout the world was performed by the GELA and compared CHOP versus Rituximab-CHOP (R-CHOP) in elderly patients (21,22). The GELA group randomized 399 previously untreated patients with DLBCL, 60 to 80 years old, to receive either 8 cycles of CHOP every 3 weeks or 8 cycles of CHOP plus rituximab given on day 1 of each cycle. Complete response rates of 76% and 63% (p=0.005) and 5- year overall survival rates of 58 % and 45 % (p< 0.007) were achieved by R-CHOP and CHOP, respectively. In patients with a low- risk age adjusted IPI (0 or 1 adverse prognostic factors), 5-year event-free survival (EFS) was 63% and 34% for the R-COP and CHOP arms, respectively (p=0.0008). For those with high-risk disease (2, 3 adverse factors), 5 year EFS were 41% and 27% for the R-CHOP and CHOP arms, respectively (p=0.004). These results suggest that addition of rituximab therapy to standard CHOP may lead to significant prolongation of event-free and overall survival in elderly patients with both high-risk and low risk disease with no increase in toxicity. In an early analysis, R-CHOP appeared to be more effective than CHOP in bcl-2 positive, but not in bcl-2 negative patients, suggesting that the benefit of addition of rituximab might overcome bcl-2 associated chemotherapy resistance (23,24).

In the United States a larger (N=632) intergroup study randomized elderly patients to receive initial therapy with either CHOP or R-CHOP. The rituximab was given on a different schedule than the GELA study. Responding patients then were randomized to receive either rituximab maintenance therapy (4 doses q 6 months x 2 years) or no maintenance. This study confirmed the GELA results with a significant advantage for receiving rituximab either in during induction or maintenance, but no advantage to getting both (25).

According to the IPI young good prognosis patients comprise the low and low-intermediate risk group (0 and 1 risk factor according to the age-adjusted IPI) and poor prognosis patients the high-intermediate and high risk group (2 risk factors).

Until recently there was no Phase III trial looking for the value of rituximab in younger patients with DLBCL. An International study called MInT Trial compared chemotherapy CHOP with or without rituximab in patients younger than age 60. Eligibility criteria included DLBCL, 18-60 years, IPI 0 or 1, stages II-IV or stage I with bulk. Patients received 6 cycles of any of several CHOP like regimens followed by radiation therapy to bulky disease (9). The MInT trial demonstrated significant advantage in response, failure-free survival, and overall survival with the addition of rituximab.

The German High Grade Lymphoma Study Group (DSHNHL) studied the utility of six versus eight cycles of R-CHOP at 14 day intervals with or without rituximab in elderly patients with DLBCL. RICOVER 60 trial of DSHNHL demonstrated the importance of rituximab and in combination with rituximab 6 cycles of R-CHOP-14 are as good as 8 cycles.(26)

Investigators from the Cancer Institute from the British Columbia did a population based study of the impact of adding rituximab to CHOP. After approval of rituximab in British Columbia survival of DLBCL went up of about 20%.(27)

III. Treatment Of Young, High Risk Patients

According to the IPI, young poor prognosis patients comprise the high-intermediate and high risk group (aa IPI 2,3). For young poor prognosis patients, the five-year survival is around 50%,

and progress has not been demonstrated in these patients.

The role of high-dose therapy (HDT) followed by autologous stem cell transplantation (SCT) for primary treatment of aggressive non-Hodgkin lymphoma is still uncertain. Whereas some studies demonstrated superiority of HDT over conventional treatment (28, 29,30), others failed to show significant differences (31,32,33) or reported inferior results (34). Besides differences in patient characteristics, the type HDT and its timing may have important implications for outcome. Recently published meta-analysis showed that there was no evidence that HDT improved OS and EFS in good risk NHL patients. The evidence for poor risk patients is inconclusive and high quality studies in poor risk patients are warranted (35).

Recently, German High Grade NHL study group published the result of Mega CHOEP chemotherapy. The Mega CHOEP protocol consisted of 4 courses of Cyclophosphamide, doxorubicin, vincristine, etoposide and prednisolone. MegaCHOEP was applied as high dose chemotherapy including autologous stem cell transplantation after courses 2, 3, 4 .The patients aged 18-60 years with primary diagnosis of aggressive NHL and LDH levels above normal were included in the study. 70% of the patients achieved CR or CRu after a median follow-up of 55 months. OS was 75 % and 67.2 % after 2 and 5 years, respectively. Treatment related mortality was 4.5%. Risk of secondary MDS/AML was low with only one patient having MDS during follow up.

Comparison of the results of Mega CHOEP with R-CHOP chemotherapy is difficult. The only study published with R-CHOP chemotherapy was that of British Columbia's and 4 year OS was 55% for this high risk patient group. But we have to keep in mind that the median age of this group was older (median age 61) than the patients included in the Mega CHOEP study (median age 43).

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