Diffuse Large-Cell Lymphoma Part II: Management

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Diffuse large-cell lymphoma (DLCL) is one of the most chemotherapy curable neoplasm. Even in patients who present with metastatic disease, an appreciable and increasing percentage can be cured. However, not all patients are cured. Furthermore, there is no absolute consensus as to which is the best current treatment strategy. Despite this uncertainty, several therapeutic principles can be identified. These principles include the following: 1) for a regimen to be curative in a substantial number of patients, it must achieve a high complete remission rate; 2) cure ideally must be accomplished with frontline therapy; 3) drugs must be delivered at effective doses which usually means maximum tolerated doses; 4) the rapidity of achieving a complete response appears to be related to probability of cure; 5) prolonged maintenance treatment for diffuse large-cell lymphoma so far has not yielded any benefit; 6) therapy is toxic and clinicians as well as patients need to understand and accept this fact; 7) follow-up for more than two years is desirable in order to interpret clinical trials since late relapses can occasionally occur and initial very positive results might decay with longer follow up and larger numbers of patients.

The first major advance in the management of DLCL consisted of the introduction of the CHOP regimen (cyclophosphamide, doxorubicin, vincristine, and prednisone), by Gottlieb, et al. in 1973 (1). This regimen, which was originally designed and piloted at MD Anderson Cancer Center, was later on tested in the Southwest Oncology Group (SWOG), which confirmed its activity in a larger number of patients (2). The study suggested that doxorubicin, a new chemotherapy agent at that time, was very effective for the treatment of advanced malignant lymphoma. The response rate seen with CHOP as well as the duration of responses were particularly encouraging and this represented a major advance in the management of non-Hodgkin's lymphoma (2). The CHOP combination achieved 4 year disease free survival rates in the range of 35 to 45 percent. Following the introduction of the CHOP regimen, for three decades there were no further substantial advances in the treatment of DLCL.

Recently, however, several clinical trials from France and Germany have demonstrated very significant improvements in clinical outcomes. In this review we will summarize these studies, attempt to objectively interpret their results and put them into the proper perspective.

The CHOP regimen, considered as a first generation combination, achieved a cure rate of approximately 30-40 percent in patients with advanced stages of DLCL in national cooperative-group trials (2-3). However, single institutions studies in the 1980s suggested that 55 to 65 percent of patients could be cured with newer "third-generation" regimens such as m-BACOD, ProMACE-CytaBOM, and MACOP-B (4-6). In order to make a valid comparison of these regimens, the Southwest Oncology Group (SWOG) and the Eastern Cooperative Oncology Group (ECOG) carried out a prospective, randomized phase III trial comparing these three combinations (3). There was no subgroup of patients in which survival was improved by any of these new third-generation regimens. Involuntary selection of a favorable group of patients at single institutions probably accounted for the inferior results obtained in the randomized SWOG trial. Some prognostic factors such as younger age patients were over-represented in some of these third generation regimens carried out at single institutions. If prognostic factors had been applied to interpret the results of trials with third generation regimens at single institution, this fiasco perhaps could have been avoided.

Management of early stage DLCL

Rituximab was introduced a decade ago for management of indolent lymphomas (7-8). It is a monoclonal antibody directed against the CD20 antigen which is expressed in the surface of most B cell lymphomas. Later on it was shown to also have activity against DLBCL (9).

Prior to the Rituximab era the standard therapy for limited or early stage I-II-A DLBCL consisted of three courses of chemotherapy using CHOP plus involved-field radiotherapy (10). A randomized study prior to the Rituximab era had shown that this abbreviated treatment consolidated by radiation rather than extended

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chemotherapy such as six or eight courses of CHOP without radiation, is superior and is associated with a 77% failure free survival at 5 years (10). Nowadays R-CHOP (Rituximab plus CHOP) rather than CHOP would be recommended for these patients. However, there are no data for three courses of R- CHOP chemotherapy with radiation consolidation for limited stage disease. In view of the activity of R-CHOP in more advanced disease (see next section below) and in spite of the lack of a randomized trial to demonstrate its superiority in the setting of three rather than six courses, most everyone prefers to use R-CHOP rather than CHOP.

R-CHOP has become the preferred chemotherapy regimen for the treatment of patients with early stage DLBCL after the MINT trial (see below) proved its efficacy in favorable risk patients. However, that trial used more than three courses of chemotherapy. Clinicians should be cautious as to the use of three courses only (11). In our opinion, it should be used only in the most favorable circumstances, i.e. in patients with non-bulky stage I disease with low LDH where it has been shown to be associated with 90% failure free survival (11).

Management of advanced stage DLCL

After Rituximab was found to have activity in B cell NHL, Coiffier, et al., from the GELA Group in France, conducted a randomized trial to compare CHOP alone vs. CHOP plus Rituximab ("R-CHOP") in patients 60 to 80 years old with DLCL-B (12). Chemotherapy courses were given every 21 days as originally described by Gottlieb, et al. Patients were randomly assigned to receive either eight cycles of CHOP every three weeks (197 patients) or eight cycles of CHOP plus Rituximab given on day 1 of each cycle (202 patients). The CR rate was significantly higher in the group that received R-CHOP as compared with the group that received CHOP alone (76 percent vs. 63 percent, P=0.005). With a median follow-up of two years, event-free and overall survival times were significantly higher in the R-CHOP group (P<0.001 and P=0.007, respectively). They concluded that the addition of Rituximab to the CHOP regimen increases the complete-response rate and prolongs event-free and overall survival in patients 60-80 years old with DLCL-B, without a clinically significant increase in toxicity.

In an attempt to improve on the results obtained with CHOP given every 21 days, Pfreundschuh, et al. investigated the use of more dose dense chemotherapy. In that trial, the same total dose of chemotherapy was given over a shorter period of time, i.e. every 14 days, with growth factor (G-CSF) support (13). This became known as the CHOP-14 regimen. To determine whether CHOP-14 with or without added etoposide is more effective than CHOP-21, 689 patients ages 61 to 75 years were randomized in the NHL-B2 trial to 6 cycles of CHOP-21, CHOP-14, CHOEP-21 or CHOEP-14. Complete remission rates, event free survival and overall survival are summarized in Table 1. The CHOP-14 and CHOEP-14 arms were collapsed into a single arm denominated CHOP-14 for the purpose of statistical analysis. Similarly the CHOP-21 and CHOEP-21 arms were also collapsed into one single arm denominated CHOP-21. Five-year event-free and overall survival rates are summarized in Table 1.

Table 1. Summary of Results of NHL-B2 Trial

	CHOP-21	CHOEP-21	CHOP-14	CHOEP-14
CRR*	60.1%	70.0%	76.1%	71.6%
5 Years EFS**	32.5%	-	43.8%	-
OSR***	40.6%	-	53.3%	-

*CRR= complete response rate
**EFS= event free survival
***ORR= overall survival rate

Interestingly, the biggest impact was observed in the group with high pretreatment LDH (Table 2). It is a well known fact that elevated LDH is associated with aggressive behavior and particularly with higher grade histologies. Perhaps this dose dense regimen might be more effective in those aggressive histologies with highly proliferative tumors which we frequently associate with tumor growth in between courses of therapy. Shortening the treatment intervals to every 14 rather than 21 days might benefit these patients preferentially.

Table 2. Complete response rate according to LDH level

	Complete Response Rates			
Regimen	**PT**	**ALL**	**LDH normal**	**LDH high**
Patients	728	728	392	336
CHOP-14	179	77	85	68
CHOEP-14	180	74	79	68
CHOP-21	189	63	79	45
CHOEP-21	180	72	82	60

Pfreundschuh, et al. concluded that, due to its superior efficacy and toxicity profile, CHOP-14 should be considered as the new standard chemotherapy regimen for patients 60 years or older (13).

Leukopenia of grades 3 and 4 did not occur more frequently in the CHOP-14 than in the CHOP-21 cohort most likely because of the use of G-CSF in the 14 day regimens. The neutrophil nadirs occurred on days 10 to 12 of the cycle in the 21 day regimens and on days 8 to 10

in the 2-week regimens. Besides leukopenia, anemia and thrombocytopenia were the most frequent adverse events.

Simultaneously with the NHL-B2 trial, the same investigators conduceted the NHL-B1 trial. They tested the same four regimens as in the NHL-B2 trial but in patients aged 18 to 60 years with good prognosis (normal lactic dehydrogenase level). The goal was to determine whether the addition of Etoposide as in CHOEP can improve results over CHOP and to determine whether the 14 day regimen was superior to the conventional 21 days. A total of 710 patients were randomized to 6 cycles of CHOP-21, CHOP-14, CHOEP-21 or CHOEP-14. Patients in the biweekly regimens received G-CSF. Patients received radiotherapy (36 Gy) to sites of initial bulky disease and extranodal disease.

CHOEP achieved a higher complete remission rate (87.6% versus 79.4%; P =.003) and 5-year event-free survival rates (69.2% versus 57.6%; P =.004, primary end point) than CHOP (Table 3). Although the CHOEP regimens induced more myelosuppression, the authors considered that it should be the preferred chemotherapy regimen for patients younger than 60 with good-prognosis (normal LDH level) aggressive lymphoma (14).

Table 3. Summary of Results of NHL-B1 Trial

Outcome	CHOP-14/21 %	CHOEP14/21 %	CHO(E)P-21 %	CHO(E)P-14 %
CR*	79.4	87.6	82.5	84.6
	P = .003	P = .003	P = .477	P = .477
5-y EFS**	57.6	69.2	62.1	65.2
5-y OS***	79.9	84.1	79.2	85.0

*CR = complete response **EFS = event free survival ***OS = overall survival

The conclusions derived from both the NHL-B1 and NHL-B2 trials were from studies carried out without the use of Rituximab. Consequently, the logical next step was to compare these regimens against similar combinations but with Rituximab added.

Once the GELA group proved that R-CHOP-21 was superior to CHOP-21, Pfreundschuh, et al., decided to conduct a four arm randomized trial known as MInT (MabThera International Trial) (15), which compared CHOP, R-CHOP, CHOEP and R-CHOEP in patients with favorable prognosis diffuse large-B-cell lymphoma aged 18-60 years with no adverse risk factors or one risk factor according to age-adjusted International Prognostic Index (IPI). The GELA trial had been conducted in patients over 60 years old so this MInT study was the first one to test R-CHOP in patients under 60 years old.

After a median follow-up of 34 months, patients assigned to chemotherapy plus Rituximab had an increased 3-year event-free survival compared with those assigned to chemotherapy alone (79% vs. 59%, log-rank p<0.0001). The 3-year overall survival was also superior (93% vs. 84%, log-rank p=0.0001). Once more they proved that in patients that received chemotherapy alone without Rituximab, CHOEP was superior to CHOP, but when those cases who received chemotherapy plus Rituximab were analyzed separately, there was no difference in PFS between R-CHOEP and R-CHOP. They concluded that Rituximab added to six cycles of CHOP is an effective treatment for young patients with good-prognosis diffuse large-B-cell lymphoma (15). The addition of Rituximab to CHOP appeared to eliminate the advantage of CHOEP over CHOP. This study was also important from the standpoint that it proved for the first time that Rituximab when added to CHOP or CHOEP is effective in patients younger than 60 with favorable prognosis, which was a population totally different from that included in the GELA trial that first proved the effectiveness of Rituxan in combination with CHOP.

The RICOVER-60 trial also led by Pfreundschuh (16), consisted of a 4 way randomization between CHOP-14 x 6, CHOP-14 x 8, R-CHOP-14 x 6 and R-CHOP x 8 (Figure 1). The goals of this randomized trial were to assess whether six courses were as effective as eight cycles and whether the addition of Rituximab to CHOP-14 could improve outcome of patients treated with the CHOP-14 regimen which had been declared by them as the standard of care after completing the NHL-B2 trial. A total of 1,222 patients aged 61-80 years were randomly assigned to the above four arms. Radiotherapy was planned to sites of initial bulky disease with or without extranodal involvement. They concluded that six cycles of R-CHOP-14 significantly improved event-free, progression-free, and overall survival over six cycles of CHOP-14 treatment. The other major conclusion of this study was that six cycles of chemotherapy with or without Rituximab was as effective as eight cycles. Chemotherapy beyond six cycles, though widely practiced in Europe, is not justified any longer. Of the four regimens assessed in this study, six cycles of R-CHOP-14 is the preferred treatment for elderly patients, and is the new standard of care against which new strategies should be compared (16).

Table 4. Summary of Results of RICOVER-60 Trial

	CHOP-14 x6	CHOP-14 x8	R-CHOP-14 x6	R-CHOP-14 x8
3-year PFS*	56.9%	56.9%	73.4%	68.8%
3-year OS**	67.7%	66.0%	78.1%	72.5%

*PFS = progression free survival **OS = overall survival

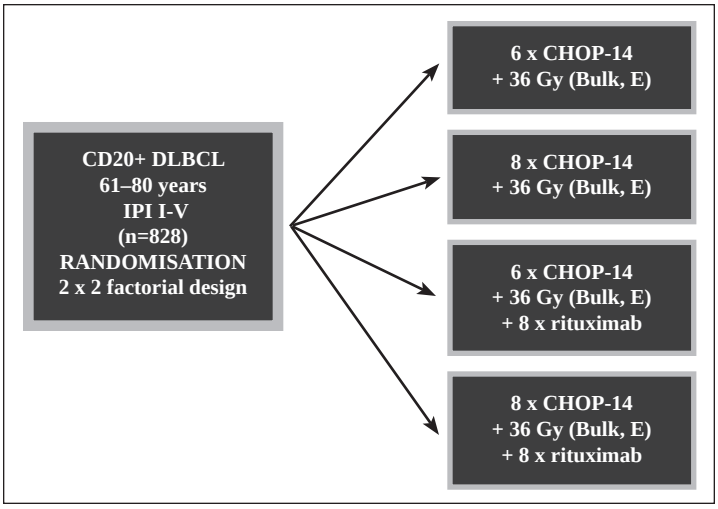


Figure 1. Design of RICOVER-60 trial.

Experience with R-CHOP-14 in Puerto Rico

From 4/11/05 to 7/8/08 we accrued a total of 54 patients with aggressive histologies to this study carried out at Auxilio Mutuo Cancer Center. Patients older than 18 years with large-cell lymphoma, either follicular or diffuse, stage I-IV were eligible for this study which was approved by the local institutional review board. Treatment consisted of R-CHOP given every 14 days with the support of PEG-Filgrastim. The doses administered were: Rituximab 375 mg/M2 IV on day 1, Cyclophosphamide 750 mg/M2 IV day 2, .Doxorubicin 50 mg/M2 IV day 2 Vincristine 1.4 mg/M2 IV day 2 (top dose 2.0 mg) and Prednisone 100 mg p.o. days 1-5. On day 3, a single 6 mg dose of PEG-Filgrastim was administered subcutaneously. Median follow up time is 20 months. Table 5 summarizes the characteristics of the 54 patients entered on this study.

Table 5. Demographics of patient population

Factor	Result
Median Age (range)	57 (25-87)
Diagnosis	
DLCL	49
FLCL	5
B cell	53
T cell	1
IPI	
0-2	37
3-5	17
Ann Arbor Stage	
I-II	24
III	11
IV	19

Projected overall survival at 3 yrs was 85% (Figure 2). Projected progression free survival at 3 yrs was 82% (Figure 3). Figure 4 depicts the progression free survival according to age and Figure 5 according to IPI.

Interestingly, age is not an important prognostic variable in this trial when the usual cut-off point of 60 years is used. Age used to be one of the most important prognostic variables but is no longer a significant factor in this study. In addition, there is no statistical significance to the small difference seen for the two IPI groups (<3 vs. >3). These data not only confirm the excellent results of the R-CHOP14 protocol but also suggest that the natural history of large-cell lymphoma has changed with this new strategy. As the prognosis improves with new treatment regimens, some of the predictive variables that used to be relevant will no longer be important. This is the most likely explanation for the lack of correlation with age and IPI in our study.

The mean interval between course 1 and course 2 was 14.5 days with 81% receiving their courses within the scheduled 14 days and 93% within 16 days. Only 11% of patients developed some type of infection; but there were no deaths secondary to infection.

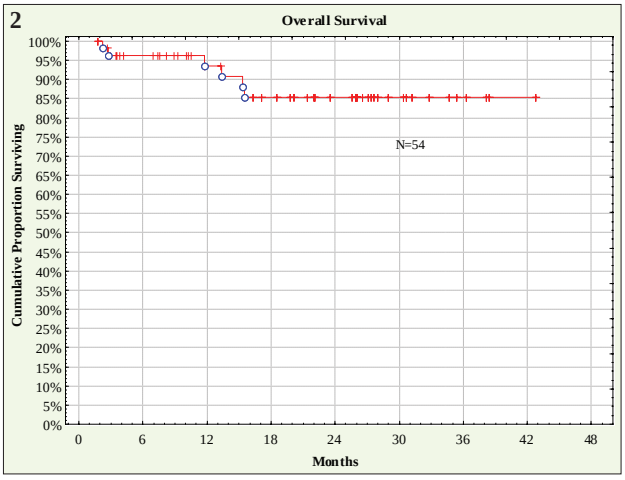
Future directions

Efforts to discover new active agents in NHL are mostly based on biological targeted therapies. Examples of potentially useful drugs are Enzastaurin, a PKC-b inhibitor (see part I of this review) which is undergoing scrutiny as maintenance therapy for patients with high risk for relapse after achieving complete remission. Other biological agents such as Ofatumumab, a new generation anti-CD20 monoclonal antibody which appears to have superior activity to Rituximab, is receiving attention and could in the future substitute Rituximab. Revlimid has also been shown to have activity against relapsed lymphoma so it is gaining interest as a potentially useful agent in combination with chemotherapy.

Conclusions

Based upon all these studies, it is now clear that:

1. Rituximab-containing CHOP or CHOP-like regimens provide superior survival to the same regimen without Rituximab, regardless of the patient's age and regardless of whether CHOP is given every 14 or 21 days.
2. Six cycles of chemotherapy are as effective as eight.



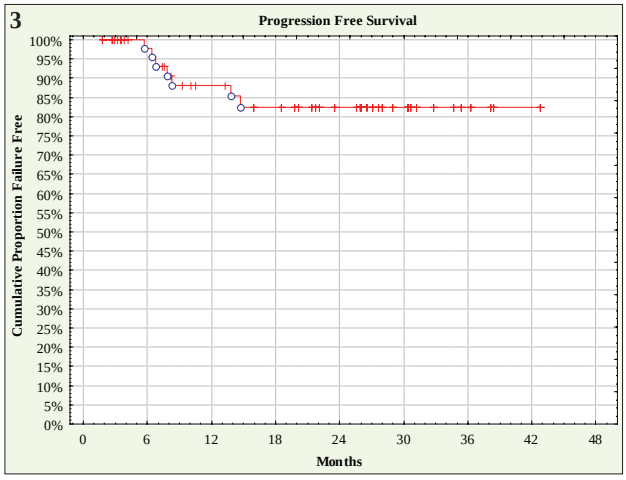


Figure 2 & 3. Overall survival of patients treated with R-CHOP-14 in Puerto Rico.

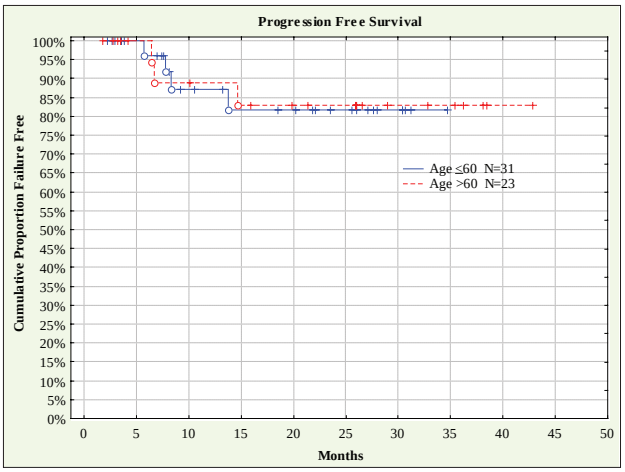


Figure 4. Progression free survival of patients treated with R-CHOP-14 in Puerto Rico according to age.

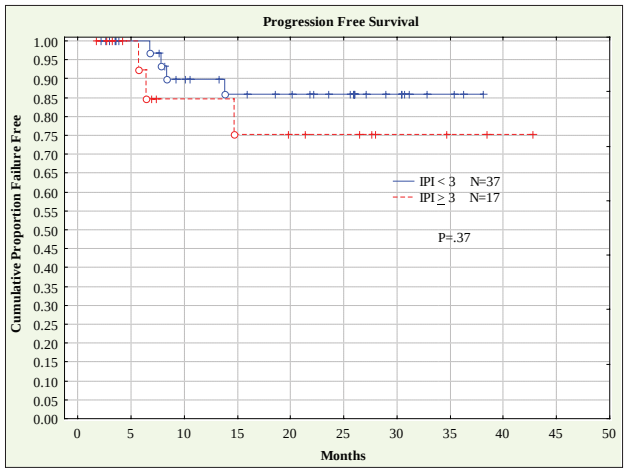


Figure 5. Progression free survival of patients treated with R-CHOP-14 in Puerto Rico according to IPI.

3. CHOP given every 14 days is superior to CHOP given every 21 days.
4. CHOP-14 has an acceptable toxicity profile.

Although it is clear that R-CHOP-14 is superior to CHOP-14, the Ricover trial has been criticized for not including an arm with R-CHOP-21. Since CHOP-14 is superior to CHOP-21, and R-CHOP-14 is superior CHOP-14 it is logical to think that R-CHOP-14 should also be superior to R-CHOP-21. However many investigators refuse to accept that R-CHOP-14 is the gold standard for treatment of DLCL until a randomized study with a control arm of R-CHOP-21 is carried out. Another reason why many clinicians have not embraced R-CHOP-14 is because of fear that it is too toxic. However, the NHL-B2 trial showed that CHOP-14 was actually less myelosuppressive than CHOP-21 most likely because of the use of growth factor support. One point that should be kept in mind is the possibility that the every 14 day dose dense regimen is more immunosuppressive in view of the description of Pneumocystis carinii pneumonia by Brusamolino et al from Italy. Prophylaxis with Trimetropin-Sulfa twice per week should be considered for patients receiving the dose dense schedule.

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