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Competitive Treatment in Diffuse Large B-cell lymphoma (DLBCL) and the Future SOC for the First Line Therapy

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Abstract

Diffuse large B-cell lymphoma (DLBCL) in the most common type of non-Hodgkin's lymphoma (NHL) in developed world, so far and approximately 60,000 new non-Hodgkin lymphoma (NHL) cases and 20,000 deaths have been estimated in the United States for 2010. In spite of novel therapeutic options have been suggested and successfully tried in patients with lymphoproliferative disorders, the standard first- line treatment for DLBCL has remained the same combination of chemotherapy and CD20 (activated-glycosylated phosphoprotein) targeting monoclonal antibody rituximab (R) with 30% to 40% chance of relapse after first line R-CHOP treatment. Several clinical trials have been designed to evaluate safety, efficacy and superior clinical benefit by adding novel agents, intensifying cycles of treatment or substituting rituximab with new CD20 targeting immunotherapies. Intensification of cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) chemotherapy from 3- week interval cycles to 2- week interval cycles has already shown clinical benefit in a German trial but failed to show improved overall and disease free (DFS[1]) survival in both elderly (60 to 80 years) and young patients in randomized phase 3 clinical trials. Namely, in a phase 2 randomized clinical trials (PYRAMID) as a first line treatment for non- Germinal Center Cell (GCB) subtype of DLBCL the results were in favor of R-CHOP and adding bortezomib was not found to improve DFS and OS significantly. Immunomodulatory agent lenalidomide is another attractive therapeutic option for non-GCB subtype of DLBCL. Statistically significant difference between non-GCB and GCB controls treated with standard R-CHOP alone in terms of progression-free survival (28% vs. 64%; P = 0.00029) and overall survival (46% vs. 74%; P = 0.000036) was reported while non-GCB and GCB treated with R-CHOP plus lenalidomide had similar rates of progression (60% vs. 59%; P = 0.83) and overall survival at 2 years (83% vs. 75%; P = 0.61). Despite these promising clinical results, further clinical studies, especially phase 3 randomized clinical trials are required to confirm the alternate competitive treatment for DLBCL patients.

Keywords: CD20 targeting monoclonal antibody rituximab; Chemo-immunotherapy; Dose-intensive rituximab; Doxorubicin; Cyclophosphamide; Vindesine; Bleomycin; Prednisone; Lenalidomide; mTOR inhibitor everolimus; Obinutuzumab; Ibrutinib; Brentuximab-vendotin; Progression-Free Survival (PFS); Overall Survival (OS)

[1] In cancer, the length of time after primary treatment for a cancer ends that the patient survives without any signs or symptoms of that cancer. In a clinical trial, measuring the disease-free survival is one way to see how well a new treatment works. Also called DFS, relapse-free survival, and RFS.

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Introduction

Diffuse large B cell lymphoma (DLBCL) in the most common type of non-Hodgkin's lymphoma (NHL) in developed world, so far. New molecular studies have divided this this lymphoproliferative disorder into two major categories (PFS[2]); activated B cell (ABC) and germinal center cell (GCB) subtypes. In general, ABC subtype presents with poor outcome compared to GCB subtype [1-3]. Besides, there is a more aggressive subtype of DLBCL which has been reported to be 5% to 10% of all DLBCL cases and presents with both MYC and BCL2 or BCL6 gene re-arrangement and is so called double hit lymphoma [4]. Despite novel therapeutic options have been suggested and successfully tried in patients with lymphoproliferative disorders, the standard treatment for DLBCL has remained the same combination of chemotherapy and CD20 targeting monoclonal antibody rituximab with 30% to 40% chance of relapse after first line R-CHOP treatment. Elderly and frail patients may not tolerate this anthracycline based combination chemotherapy and either modification in the dose or replacing anthracycline with less cardio-toxic chemotherapeutic agent have been suggested for this group of patients **(Table 1)** [5]. Several clinical trials have been designed to evaluate safety, efficacy and superior clinical benefit by adding novel agents, intensifying cycles of treatment or substituting rituximab with new CD20 targeting immunotherapies compared to the standard R-CHOP combination chemo-immunotherapy that is given every 21 days.

Examples for the novel agents include the following **(Table 2)** [6]: Intensification of CHOP chemotherapy from 3-week interval cycles to 2-week interval cycles has already shown clinical benefit in a German trial in patients older than 60 in pre-rituximab era [7]. However, intensified R-CHOP chemotherapy in a 2-week interval has failed to show improved overall and disease-free survival in both elderly (60 to 80 years) (the LNH03-6B study) and young patients in randomized phase 3 clinical trials [8,9]. Clinical benefit of adding etoposide to the R-CHOP backbone in R-dose adjusted EPOCH combination chemo-immunotherapy has also been evaluated in both phase 2 and phase 3 clinical trials. Despite the excellent phase 2 trial results reporting the time to progression and event-free survival of 100% and 94%, in GCB (Germinal Center Cell) subgroup and 67% and 58% in non-GCB cases of DLBCL at 62 months follow up, this combination has failed to show superior results in terms of DFS and OS between two study groups. Besides, more patients in DA-R-EPOCH were unable to complete course of treatment due to toxicity [10,11].

Literature Review

The concept of intensifying chemotherapy for better DFS and OS has also been validated in phase 3 clinical trial (LNH03-2B) by using R-ACVBP (dose-intensive rituximab, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone) followed by consolidation in adult patients with DLBCL below the age of 60 compared with standard R-CHOP. This study showed superior 3-year event free survival of 81% (95% CI 75-86) vs. 67% (59-73) in R-ACVBP study group in low and intermediate risk DLBCL patients. 3-year estimates of progression-free survival was 87% (95% CI, 81-91) vs. 73% (66-79); HR 0.48 (0.30-0.76); p=0.0015) and overall survival 92% (87-95) vs. 84%. However, serious adverse events were 3 times in study group (42% vs. 15%) with 38% incidence of febrile neutropenia in R-ACVBP group **(Tables 3 and 4)** [12]. Poor outcome of non-GCB subtype has suggested the possibility of improving DFS and OS by adding novel treatment modalities to the classic R-CHOP combination. Considering the molecular pathways responsible for tumor genesis and promotion of non-GCB subtype of DLBCL involving nuclear factor-kb, proteasome inhibitor bortezomib, specifically targeting this pathway considered to be an attractive novel agent which combined with R-CHOP may potentially improve DFS and OS in this specific subgroup of patients. However, several phase 2 clinical trials have failed to show clinical benefit in terms of

Table 1 Doses of chemotherapy regimens.

S. No	Regimen	Dose
1	Rituximab	375 mg/mg^2
2	Cyclophosphamide	750 mg/m^2
3	Doxorubicin	50 mg/m^2
4	Vincristine	1·4 mg/m^2
5	Prednisone	40 mg/m^2

Table 2 Examples for the novel agents.

S.No	Agents	Examples
1	Immunomodulators	Pomalidomide
2	Proteasome inhibitors	Carfilzomib, Marizomib, Ixazomib, Oprozomib
3	Alkylating agents	Bendamustine
4	Akt inhibitors	Afuresertib
5	Btk inhibitors	Ibrutinib
6	Cdk inhibitors	Dinaciclib
7	Histone deacetylase inhibitors	Panobinostat, Rocilinostat, Vorinostat
8	Il-6 inhibitors	Siltuximab
9	Kinesin spindle protein inhibitors	Filanesib
10	Monoclonal antibodies	Daratumumab, Elotuzumab, Indatuximab

Table 3 Details with different regimens.

S.No	Regimen	Drugs
1	DA-R-EPOCH	Darbepoetin alfa, Rituximab, Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin
2	R-ACVBP	Rituximab, Doxorubicin, CycloPhosphamide, Vindesine, Bleomycin, And Prednisone
3	EPOCH	Etoposide, Prednisone, Vincristine, Cyclophosphamide, Doxorubicin
4	R-CHOP	Rituximab, Doxorubicin, Cyclophosphamide, Vincristine, And Prednisone
5	R-CVP	Cyclophosphamide, Prednisone and Vincristine

[2] **Progression-free survival (PFS)** is defined as the time elapsed between treatment initiation and (1) metastatic tumor progression - but note NOT local or regional progression - or (2) death from any cause, with censoring of patients who are lost to follow-up (numerous others to same effect). With PFS therefore we are concerned only with distant, not locoregional, disease progression, and with death from any cause (like RFS (recurrence-free survival)).

DFS and OS. Differences in PFS and OS in patients with germinal center B-cell–like versus non-germinal center B-cell–like DLBCL were analyzed and 2-sided 95% CIs were calculated. PFS and OS data were presented as Kaplan-Meier estimates in the **(Figures 1 and 2)** namely, in a phase 2 randomized clinical trial (PYRAMID) as a first line treatment for non-GCB subtype of DLBCL the results were in favor of R-CHOP and adding bortezomib was not found to improve DFS and OS significantly.

Table 4 Analysis of endpoints in the intention-to-treat population.

Events for event-free survival	R-ACVBP group 40 (20%)	R-CHOP group 63 (34%)
Unplanned treatment for lymphoma	15	14
Unplanned chemotherapy	13	10
Unplanned radiotherapy	2	4
Progression or relapse	19	43
Death	6	6
Events for progression-free survival	**28 (14%)**	**51 (28%)**
Progression of relapse	21	44
Death	7	7
Events for overall survival	**15 (8%)**	**31 (17%)**
Lymphoma*	8	22
Unrelated to lymphoma progression during treatment	5	3
Unrelated to lymphoma progression after treatment		
Second cancer	-	2
Cardiac cause	1	-
Pneumonitis	-	2
Gastric hemorrhage	-	1
Suicide	-	1
Unknown	1	-

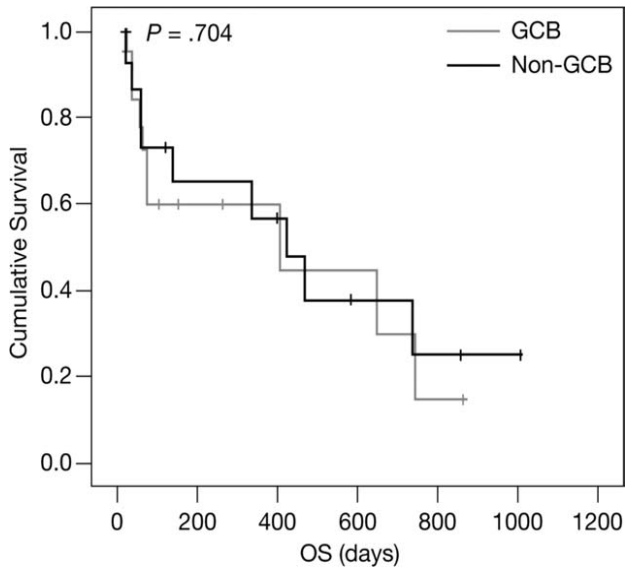

Figure 1 Overall survival (OS) of patients treated with lenalidomide monotherapy was not different between patients with diffuse large B-cell lymphoma with germinal center Bcell–like (GCB) or non-GCB phenotypes.

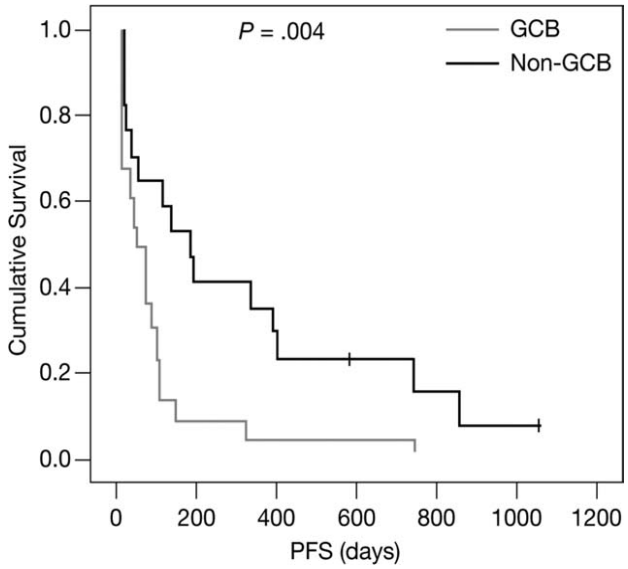

Figure 2 Patients with relapsed/refractory diffuse large B-cell lymphoma with non-germinal center B-cell–like (non-GCB) phenotype have a longer progression-free survival (PFS) than patients with GCB phenotype after lenalidomide monotherapy.

Similar results has been reported in the United Kingdom REMoDLB clinical trial in which patients were randomly assigned after the first R-CHOP treatment to receive either R-CHOP Alone or in combination with bortezomib. There was still no difference in overall response rate or CR rates between R-CHOP and R-CHOP plus bortezomib, whereas the 2-year PFS at 78% was again higher than expected and interestingly identical in both the PYRAMID and GOYA studies **(Table 5)** [13-15]. Immunomodulatory agent lenalidomide is another attractive therapeutic option for non-GCB subtype of DLBCL.

Results and Discussion

Preclinical studies have demonstrated that lenalidomide selectively kills ABC lymphoma cells by augmenting interferon beta production. This augmentation is mediated through lenalidomide effects on interferon regulatory factor 4. After superior results of treatment with lenalidomide in relapsed, refractory DLBCL of non-GCB, phase 2 randomized clinical trial studied efficacy of adding oral lenalidomide to R-CHOP clearly showed that adding lenalidomide could overcome DFS and OS difference between non-GCB vs. GCB subtype of DLBCL that has been observed in patients received R-CHOP.

Statistically significant difference between non-GCB and GCB controls treated with standard R-CHOP alone in terms of progression-free survival (28% vs. 64%; P = 0.00029) and overall survival (46% vs. 74%; P = .000036) was reported while non-GCB and GCB treated with R-CHOP plus lenalidomide had similar rates of progression (60% vs. 59%; P = 0.83) and overall survival at 2 years (83% vs. 75%; P = 0.61). Similarly, an open label, phase 2 clinical trials in elderly patients with newly diagnosed DLBCL (REAL07) reported a response rate of 92% and found the combination safe and effective in elderly group of patients **(Table 6)** [16-18].

Lenalidomide has also been introduced as maintenance treatment for 24 months in elderly DLBCL patients achieving complete response with primary R-CHOP treatment in a phase 3 randomized clinical trials versus placebo (REMARC). This maintenance treatment showed significantly prolonged DFS in study group. This DFS improvement has been associated with higher chance of grade 3 or 4 neutropenia as well as higher chance of treatment discontinuation due to adverse effects (36% vs. 16%). Besides, no beneficial on OS has been observed with maintenance lenalidomide [18]. Unlike lenalidomide, two other phase 3 randomized clinical trials using mTOR inhibitor everolimus versus placebo for one year (PILLAR-2) and oral protein kinase Cβ inhibitor enzastaurin versus placebo for 3 years and showed no difference in PFS/OS [20,21] 36% and 30% patents in the study group in both REMARC (lenalidomide) and PILLAR-2 (everolimus) maintenance clinical trials discontinued treatment early due to the adverse events, respectively [19,20].

Considering more potent antibody-dependent cellular toxicity and greater induction of apoptotic effect that has been observed with obinutuzumab compared with rituximab, substituting obinutuzumab for rituximab has been evaluated in phase 2 and 3 clinical trials. GATHER has been the phase 2 clinical study of frontline treatment with obinutuzumab plus CHOP (G-CHOP) in newly diagnosed patients with advanced DLBCL that showed ORR of 88% and manageable toxicity. However, phase 3 clinical study of G-CHOP versus R-CHOP in newly diagnosed DLBC demonstrated no difference in relative progression-free survival (PFS) that was considered the primary end point. Moreover, higher rate of toxicity and particularly dose reductions and/or dose skipping in the obinutuzumab-CHOP (G-CHOP) arm were noted. The most commonly reported adverse event in obinutuzumab arm was infusion related reaction **(Table 7)** [21,22].

Ibrutinib, small molecule bruton kinase inhibitor which has already been approved in lymphoproliferative disorders, namely mantle cell lymphoma and chronic lymphocytic leukemia. An early phase 1b clinical trial in newly diagnosed patients with DLBCL showed 100% response in non-GCB subtype DLBCL. An ongoing phase 3 clinical trial (PHOENIX) is to evaluate the efficacy of ibrutinib plus R-CHOP with placebo plus R-CHOP in newly diagnosed non-GCB-subtype DLBCL. This trial has completed patient recruitment. The primary endpoint of the study is EFS [23,24].

Antibody-drug conjugate brentuximab-vendotin targeting CD30 expressing lymphomas have already been approved in aggressive T cell lymphomas and Hodgkin's disease in relapse, refractory setting. Safety and efficacy of brentuximab-vendotin in newly diagnosed DLBCL has been evaluated in a phase 2 randomized clinical study in combination with R-CHOP versus R-CHP (without vincristine) combination chemotherapy in intermediate-high and high risk clinical setting. In part 1 of this study, 51 patients were recruited to receive brentuximab vedotin 1.2 or 1.8 mg/kg plus CHOP. In part 2, patients with CD-30 expressing high-intermediate or high risk DLBCL enrolled to receive brentuximab vedotin 1.8 mg/kg plus RCHP. First part of this trial demonstrated the estimated 24-month progression-free survival of 79% for patients with CD30 expression compared with 52% among patients without detectable CD30 expression; 24-month overall survival was 92% (95% CI, 71-98) vs. 67% (95% CI, 44-82), respectively. Of note, 73% of patients receiving brentuximab-vendotin in combination with R-CHOP presented treatment emergent peripheral neuropathy. Overall response rate for brentuximab-vendotin combined with R-CHP was reported to be 91%. Despite this promising clinical result, further clinical studies, especially phase 3 randomized clinical trials are needed to confirm the results of this early clinical study [25].

The anticonvulsant valproate in combination with R-CHOP in primary treatment of diffuse large B-cell lymphoma (DLBCL) stage II-IV, including a dose expansion cohort was initiated as an open label trial. R-CHOP was given at standard dose in 14 or 21 day cycles, 6 cycles. Valproate was given in escalating doses days 1-3, starting at 10 mg/kg every 8 hrs, by a standard 3+3 design. Prednisone was given days 1-5, R-CHOP on day 3. Response was evaluated according to the Lugano criteria. The primary outcome measure was establishment of maximum tolerable dose of valproate. Sensitization to rituximab and CHOP by pre-treatment with a Histone Deacetylase Inhibitors (HDAC) inhibitor which is a novel therapeutic strategy for the treatment of DLBCL. At a dose of 60 mg/kg, divided into 3 doses, the combination of valproate with R-CHOP is feasible in 1st line treatment of DLBCL. Higher doses of valproate were associated with intolerable auditory side effects. Early data show promising efficacy, which may form the basis for a randomized phase III trial. The long-term efficacy of this regimen remains to be established by longer follow-up.

Table 5 R-CHOP and Bortezomib treatment response.

Response	DLBCL			MCL		
	No. of Patients	%		No. of Patients	%	
		ITT (n – 40)	Evaluable (n = 35)		ITT (n – 40)	Evaluable (n = 35)
Overall	35	88	100	29	81	91
CR+CRu	30	75	86	23	64	72
PR	5	13	14	6	17	19
SD	0	0	0	3	8	9
PD	0	0	0	0	0	0
Inevaluable*	5			4		

Table 6 Response to lenalidomide monotherapy.

Lenalidomide cycles	GCB	Non-GCB
Median	2	4
Range	Jan-21	Jan-35
Response[a]		
CR	1 (4.3)	5 (29.4)[b]
PR	1 (4.3)	4 (23.5)
SD	7 (30.4)	0
PD	14 (60.9)	7 (41.2)
Unknown	0	1 (5.9)[c]
ORR (CR + PR)	2 (8.7)[d]	9 (52.9)[d]
PFS, mo		
Mean	3.3[e]	10.8[e]
95% CI	1.2-5.4	5.3-16.2
Median	1.7[e]	6.2[e]
95% CI	0.3-3.1	2.9-9.6

Table 7 Summary of efficacy end points (intent-to-treat population) for G-CHOP v R-CHOP.

End Points	G-CHOP (n = 706)	Investigator Assessment	R-CHOP (n = 712)
Median observation time (range), months	29.0 (0.1-56.6)	---	28.9 (0.1-56.2)
Investigator-assessed PFS (primary end point) Patients with event, No. (%)	**n = 706**	**---**	**n = 712**
3-year PFS, %	201 (28.5)	---	215 (30.2)
Stratified HR (95% CI); P (log-rank)*	69.6	0.92 (0.76 to 1.11); P = 0.3868	66.9
OS patients with event, No. (%)	**n = 706**		**n = 712**
3-year OS, % (95% CI)	126 (17.8)		126 (17.7)
Stratified HR (95% CI)*	81.2 (77.9 to 84.1)	1.00 (0.78 to 1.28)	81.4 (78.1 to 84.3
DFS patients with event, No. (%)	**n = 397**		**n = 369**
CR Patients with investigator-assessed Stratified HR (95% CI)*	77 (19.4)	1.27 (0.91 to 1.77	64 (17.3)
Investigator-assessed EFS Events, No. (%)	**n = 706**		**n = 712**
Stratified HR (95% CI)*	236 (33.4)	0.92 (0.77 to 1.11)	250 (35.1)
Investigator-assessed response (with PET) at end of treatment†	**n = 669**		**n = 665**
ORR Proportion, No. (%) Percentage difference (95% CI)	518 (77.4)	20.47 (25.01 to 4.08)	518 (77.9)
CR Proportion, No. (%) Difference (95% CI)	379 (56.7)	22.90 (28.27 to 2.48)	396 (59.5)

Results showed in the phase I portion, the MTD of valproate was established as 20 mg/kg every 8 hrs (total 60 mg/kg). Toxicity was comparable to that of standard R-CHOP, without any impact on hematological toxicity. At the time of this report, the study is ongoing. After a median time of follow-up of 16 months, median PFS has not been reached out of 17 evaluable patients, and estimated PFS at 18 months is 77%.

Common adverse events noticed at a dose of 80 mg/kg, 2 of 3 patients experienced tinnitus (grade 1 and 2) during the latter part of the treatment course. At a dose of 100 mg/kg, 1 of 5 patients developed hearing impairment, grade 1, after 3 cycles, which worsened to grade 2 after 4 cycles, leading to omission of valproate. One patient has died due to progressive lymphoma, 21 months after inclusion. By flow cytometry of fine needle aspirates from lymphoma lesions before and after 3 days of valproate, we could show significant upregulation of CD20 expression in 3 patients [25-27].

The study is still ongoing. One open label trial was initiated to compare the efficacy and safety of Inotuzumab Ozogamicin in combination with R-CVP (Rituximab- Cyclophosphamide, Prednisone and Vincristine) with that of R-G-CVP for the treatment of Diffuse Large B Cell Lymphoma (DLBCL) in a population of patients not suitable for anthracycline based chemotherapy. There is no standard of care for the treatment of this group of patients. If demonstrated to be efficacious and safe to deliver this regimen will be further tested in a phase III trial to determine whether this should become the standard of care amongst patients with DLBCL not fit for anthracycline (R-CHOP). The primary outcome of this clinical study is Progression free survival (PFS) and the secondary outcomes are Overall Response Rate (ORR), Overall Survival (OS), Treatment, Toxicity, Quality Of Life, Performance Status Post Treatment and co-morbidities of the patient. Given that about 40% of cases of DLBCL occur in patients aged over 70 and the number of co-mobilities increases with age, research to investigate the optimal treatment of DLBCL in this group of patients is needed. R-CHOP remains the standard of care for most patients with DLBCL; anthracycline use is precluded in a proportion of these patients by a high risk of developing cardiotoxicity, especially congestive cardiac failure.

Currently there is no standard of care for patients who are unfit for anthracycline treatment. It has been routine to omit the doxorubicin from R-CHOP, giving R-CVP instead. However, the outcome for patients treated with R-CVP is poor and attempts have been made to replace the doxorubicin with alternative agents. The trial will compare an experimental arm consisting of Inotuzumab Ozogamicin added to the standard immunochemotherapy regimen of rituximab, cyclophosphamide, vincristine and prednisolone (R-CVP) with the control arm of gemcitabine added to the same combination (Gem-R-CVP). Study is still ongoing and no further analysis was performed [28].

Metformin[3] as an adjunct to RCHOP chemotherapy for patients with newly diagnosed diffuse large-B cell lymphoma was assessed with an open label single group assignment treatment study for evaluation of the safety and effectiveness. The primary outcomes of incidence of treatment-emergent adverse events and response rates and secondary outcomes of progression-free survival, overall survival, event-free survival, survival from diagnosis until death or progression, time to progression or relapse. Patients with newly diagnosed diffuse large-B cell Non Hodgkin lymphoma, irrespective of cell of origin status will receive metformin in combination to Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (RCHOP) chemotherapy for 6 cycles, until response evaluation as reported. Metformin will be added and administered in an outpatient basis, starting with 425 mg twice a day for 1 week, followed by 850 mg twice a day for 1 week, and lastly 850 mg every 8 hours maximum dose

[3]Metformin is a biguanide antihyperglycemic agent used in management of Type 2 Diabetes. It improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. It decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization

until re-staging. Laboratory tests will be performed serially. Study is still ongoing and no further analysis was performed [29].

Treatment of Yt90 Zevalin[4] in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) are effective as first line treatment in patients with bulky stage II or stage III or IV diffuse large B-cell lymphoma. A non-randomised, open label single group assignment treatment study with primary outcome of 2-year progression-free survival and overall survival of patients and secondary outcomes of response rate in patient's 2-year progression-free survival, overall survival and response rate in BCL-2 positive patients was initiated. Radio-immunotherapy represents a significant advance over unlabeled immunotherapy for the treatment of patients with B-cell non-Hodgkin's lymphoma. The radio-biological effects associated with Yt90-labelled ibritumomab tiuxetan (Zevalin) include the induction of apoptosis and cell-cycle redistribution. The response rate tends to be higher in patients who have been treated with fewer prior therapies and Yt90-labelled ibritumomab tiuxetan may be suitable for use early in the course of therapy. Yt90-labelled ibritumomab tiuxetan has less non-hematologic toxicity than chemotherapy, with only minimal alopecia, mucositis, nausea, or vomiting, and a lower incidence of infections. Yt90-labelled ibritumomab tiuxetan regimen is routinely and safely given in an outpatient setting and is completed in 7-9 days and is thus more convenient to be used. This study has been terminated and no articles have been published yet [30].

Replacing doxorubicin by Myocet®[5] in the R-CHOP regimen would yield comparable antitumour efficacy with a lower cardiotoxicity for first-line treatment in elderly patients with non-localised DLBCL/Follicular lymphoma grade IIIb. An open label treatment, parallel assignment study with primary outcomes of Subclinical cardiac toxicity and subclinical cardiac toxicity and secondary outcomes of survival, response rate, cardiac/cardiovascular toxicity, toxicity (except cardiac) and cardiac biomarkers was initiated. Treatment for patients with DLBCL is currently based on immunochemotherapy, of which the R-CHOP regimen, which includes cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) in combination with the anti-CD20 monoclonal antibody rituximab and is administered every 21 days for a total of 6-8 cycles, is the most commonly used. Cardiotoxicity is one of the undesirable effects that limit the use of anthracyclines, such as doxorubicin, as part of the CHOP regimen, which is caused by the formation of complexes between ferric ions and the anthracycline within the myocyte. Myocet® (non-pegylated liposomal doxorubicin) is one of the several strategies developed to reduce cardiotoxicity and maintain the therapeutic efficacy of the R-CHOP regimen. Non-pegylated liposomal doxorubicin has shown a similar efficacy and less cardiotoxicity than conventional doxorubicin in the treatment of women with metastatic breast cancer. Most of these phase I and II studies (with or without rituximab), which assessed Myocet® in combination with cyclophosphamide; vincristine and prednisone, showed that it is an active treatment in newly diagnosed patients with aggressive NHL. Study is still ongoing and no further analysis was performed [31].

Conclusion

DLBCL is the most common type of NHL, the standard treatment with combination of rituximab and CHOP therapy is used as first line treatment. Competitive treatments that are being explored are the treatment of patients with lymphoproliferative disorders and several clinical trials have been initiated. Despite the positive results with the alterantives available for the treatment there has been showed no difference in PFS or OS in case of treatment with everolimus versus placebo for one year (PILLAR-2) and oral protein kinase Cβ inhibitor enzastaurin versus placebo [20,21]. Besides, no beneficial on OS has been observed with maintenance lenalidomide [19]. and G-CHOP did not improve PFS compared with R-CHOP in patients with previously untreated DLBCL. Although these observations may help to inform and shape the direction of future research activities in patients with advanced-stage DLBCL, the need for improved therapeutic options therefore remains.

Conflict of Interest

The authors declare that they have no conflict of interest that competes with any of the contents of the manuscript.

[4]Zevalin is a CD20-directed radiotherapeutic antibody administered as part of the Zevalin therapeutic regimen indicated for the treatment of patients relapsed or refractory, low-grade or follicular B-cell non-Hodgkin's Lymphoma previously untreated follicular NHL who achieve a partial or complete response to first-line chemotherapy

[5]Myocet, in combination with cyclophosphamide, is indicated for the first line treatment of metastatic breast cancer in adult women.

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