NEXT STEPS IN FRONT-LINE TREATMENT OF LYMPHOMA: THE ROAD AHEAD

Summary of Presentations from the Celgene-Sponsored Satellite Symposium, held at the 19th EHA Congress, Milan, Italy, on 12th June 2014

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MEETING SUMMARY

Prof Zelenetz opened the symposium on the evolving front-line treatment options for follicular lymphoma (FL) and discussed the potential of novel agents to replace chemotherapy. Prof Zelenetz presented the heterogeneity of diffuse large B cell non-Hodgkin's lymphoma (DLBCL) with regard to the diagnosis and subtypes of DLBCL to describe the specificity of new agents towards certain DLBCL subgroups, whilst Prof Dreyling spoke about the current diagnosis and treatment pathways for mantle cell lymphoma (MCL), and briefly described recent trial results. The final presenter, Prof Coiffier, discussed the lack of efficacy of front-line chemotherapy regimens for peripheral T cell lymphoma (PTCL), and highlighted potential new treatments based upon CHOP (cyclophosphamide, hydroxydaunorubicin, vincristine, prednisone). He then addressed the use of transplantation for first-line and refractory disease, and called for research to optimise therapy using existing agents.

Front-line Therapy for FL: a Shift towards Chemotherapy-Free Options?

Professor Bruce Cheson's presentation given by Professor Andrew Zelenetz

A large number of alkylating agents are currently used as first-line management of non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukaemia (CLL); however, recent data suggest that although chemotherapy improves time-to-treatment failure and progression-free survival (PFS), it does not impact overall survival (OS).[1] Bendamustine appears to improve PFS when compared to rituximab and CHOP (R-CHOP) in indolent NHL and MCLs; however, OS was not altered.[2] PFS can be improved by the addition of rituximab in the maintenance phase; however, the 6-year data again showed no difference in OS for patients with NHL or MCL.[3] Although therapies based on alkylating agents do improve PFS, there are acute and late toxicities including leukemogenesis, and many patients cannot tolerate the treatment. With the advent of novel biological combinations, the current first-line therapy for indolent lymphoma may be revised.

The Cancer and Leukaemia Group B (CALGB) undertook a series of studies that looked into immunotherapy doublets, the first of which was a Phase II trial of galiximab, an anti-CD80 monoclonal antibody (mAb), with rituximab but without chemotherapy (CALGB 50402).[4] Patients with low-risk disease according to the Follicular Lymphoma International Prognostic Index (FLIPI) showed the highest overall response rate (ORR) of 93%, with a complete response rate (CRR) of 75%, and patients with low-to-intermediate risk had a PFS in excess of 4 years with rituximab and galiximab. Patients with high-risk disease showed an ORR of 55% and a CRR of 27%.[4] The CALGB group found similar results when combining epratuzumab - an anti-CD22 mAb - with rituximab,[5] which resulted in an 86.5% response rate and a CRR of 42% after a median time of 9.2 months. However, further studies are necessary for both galiximab and epratuzumab when combined with rituximab as first-line therapy.

Chemotherapy can be used in a more targeted manner by combination with an antibody to specifically bind to the tumour cell and deliver the drug. Inotuzumab ozogamicin, an anti-CD22 mAb conjugated to calicheamicin,[6] was combined with rituximab and resulted in excellent overall and complete responses in patients with FL of 87% and 62%, respectively (n=39), whilst PFS was 39 months.[7] Other emerging antibody-drug conjugates include anti-CD22 and anti-CD79b conjugated to auristatin.[8-10] A recent study in patients with FL using two different combination therapies, showed a higher overall or objective response with anti-CD79b-rituximab (70%, n=14)[9] compared with anti-CD22-rituximab (59%, n=13)[8] and CRR (40%, n=8 versus 9%, n=2);[10] however, further evaluation is required due to the low number of patients. Grade 3/4 neutropaenia was reported by around 15% of the patients, as was some Grade 1 and 2 peripheral sensory neuropathy.[8-10]

Another approach to treat indolent lymphomas is to target tumours that have chronic active signalling through the B cell receptor and are dependent on downstream signalling pathways, which can be targeted via Bruton's tyrosine kinase (BTK), and therefore inhibited by ibrutinib.[11] Ibrutinib is known to affect other kinases; extrapolated data showed optimal CRR (33.3%, n=9) and improved PFS in patients given doses >5 mg/kg/day in a Phase I study (n=15).[12]

Activation of the B cell receptor initiates the PI3-kinase/AKT pathway, which can be targeted by numerous drugs such as idelalisib - a PI3-delta-specific kinase inhibitor. Promising initial results from Phase I and II studies[13,14] led to a small Phase Ib study to evaluate the safety of combining idelalisib with rituximab (n=32), or bendamustine (n=28), or both (n=10).[15] Improved PFS and CRRs confirmed the safety of combining idelalisib with other treatments. A further promising gamma/delta inhibitor is IPI-145, which demonstrated an ORR of 68% in patients with indolent lymphoma.[16]

Lenalidomide is another encouraging drug that has been shown to improve the immune synapse between B cells and T cells, enhance antibody-dependent cell-mediated cytotoxicity, and influence the microenvironment and angiogenesis. The wide-ranging properties of lenalidomide have a broad activity across various cancer types, as shown in Table 1.[17-20] A Phase II study of lenalidomide alone versus lenalidomide + rituximab in patients with relapsed/refractory FL showed that, although ORR was higher in the combination arm, CRRs were almost three-times higher in the lenalidomide arm, with a corresponding improvement in the event-free survival (EFS) from 1.2-2 years. Another multicentre trial of lenalidomide + rituximab for front-line treatment of FL showed a CRR of 71%.

Table 1: Response rates of lenalidamide.

	SLL (N=27)*	Marginal (N=27)*	Follicular (N=46)*	All Patients Eval (N=103)	All Patients ITT (N=110)
ORR, n (%)	24(80)	24(89)	45(98)	93(90)	93(85)
CR/CRu	8(27)	18(67)	40(87)	66(64)	66(60)
PR	16(53)	6(22)	5(11)	27(26)	27(25)
SD, n (%)	4(13)	3(11)	1(2)	8(8)	8(7)
PD, n (%)	2(7)	0	0	2(2)	2(2)

*7 patients were not evaluable for response – 5 patients due to an adverse event in cycle 1, 1 patient from non-compliance, and 1 patient withdrew consent.
CR: complete response; CRu: complete response unconfirmed; Eval: evaluable patients; ITT: intention-to-treat population; ORR: overall response rate; PD: progressive disease; PR: partial response; SD: stable disease; SLL: small lymphocytic lymphoma.
Modified from Fowler et al.[20]

Adverse events included neutropaenia Grade 3/4 in some patients who had a relatively low risk of febrile neutropaenia and thrombocytopaenia in a few patients, whilst fatigue was a very common side-effect and extensive rash is often seen in patients treated with rituximab and lenalidomide.

In summary, promising novel therapies are emerging that offer specificity as they target cell surface molecules and intracellular pathways, which may result in treatment management strategies that move away from chemotherapy. Combinations selected upon specific tumour types can be developed, thereby tailoring the therapy to each patient.

Optimising Front-line Treatment of DLBCL

Professor Andrew Zelenetz

The 2008 World Health Organization classification of lymphoid neoplasms will be amended next year to reflect the heterogeneity of DLBCL.[21] The heterogeneity of DLBCL was confirmed through gene expression profiling that identified two or three distinct subtypes of DLBCL according to the cells of origin:

1. Activated B cell (ABC) DLBCL

2. Germinal centre (GC) DLBCL

3. Primary mediastinal large B cell lymphoma (PMBCL), which tend to occur in women and show distinct molecular heterogeneity[22-26]

These heterogeneities are demonstrated by differences in patient outcomes, with superior OS and PFS shown in patients with the ABC Type.[21] Further analysis confirmed that EZH_2 overexpression seems to be a critical abnormality within the GC B cell (GCB) DLBCL;[27] whereas, NF-κB activation appears to be the hallmark of the ABC DLBCL, and the PMBCL have a unique molecular pathway. Further to the findings, there can be acquired mutations that are unique to a specific subtype; for example, only the ABC Types show mutations to CD79b.

The cells of origin can also be determined by a variety of models that include the Hans model,[28] the Choi model,[29] or the Tally model,[30-32] but these methods have a significant risk of misclassification compared to gene expression profiling on tissue. Digital multiplexed gene expression profiling uses RNA on a platform that can identify up to 800 genes per run. The Lymphoma/Leukaemia Molecular Profiling Project's Lymph2Cx assay uses formalin-fixed paraffin-embedded tissue and showed accurate assignment of ABC versus GC Types compared to the current gold standard, Affumetrix analysis, and was independently verified by two different laboratories.[31] Additionally, it provided superior identification of PFS and OS in patients compared with the Affymetrix platform,

can be performed in <36 hours, and is economically viable.[31] Fluorescence *in situ* hybridisation (FISH) can be applied to a defined set of genes where mutations have been recorded during baseline studies to further refine the profiling on several hundred DLBCL.[33]

Identification of the DLBCL subtype allows selection of the appropriate therapy, as seen in Table 2.[34] EZH2 mutations are particular to the GC DLBCL subtype, with a prevalence of ~22%. Small molecules that inhibit EZH2 are currently in preclinical testing and early clinical development.[27,35,36] ABC DLBCL are generally associated with the worst outcome; however, it was found recently, after categorising tumours for cell origin by the Hans model, that lenalidomide demonstrated an ORR of >50%.[37]

Lenalidomide not only inhibits NF-κB but also inhibits the complex IRF4 transcription factor pathway, resulting in inhibition of cell proliferation and an enhancement of cell death that has been named as synthetic lethality on ABC lymphomas.[38] A study conducted at the Mayo Clinic in elderly patients evaluated the effect of lenalidomide given for the first 10 days at 25 mg along with R-CHOP on the first day of each cycle.[39] Patient outcomes were compared to well-matched historical controls. The ORR was 98% and the CRR was 83% according to the positron emission tomography (PET) criteria (n=47).[40] Additionally, outcomes from GC and non-GC tumours were indistinguishable. Toxicity was mostly hematological with Grade 3 and 4 neutropaenia rates of 18% and 70%, respectively, 40% Grade 3/4 thrombocytopaenia, and a febrile neutropaenia rate of 10%.[39] The efficacy and safety of lenalidomide with R-CHOP has therefore led to the prospective randomised trial ECOG1412.[38,39,41]

Other targetable pathways include the B cell receptor pathway,[11] which can be treated using ibrutinib through BTK. In relapsed/refractory patients, most of the patients who responded to treatment had the ABC subtype, whilst only one patient with GC BCL responded.[42] The study further reported that a CD79b mutation upstream of BTK led to a higher ORR of 71%, whereas, a CARD11 mutation downstream of BTK predicted no response to treatment, suggesting that ibrutinib sensitivity does not require a BTK mutation. A Phase Ib study of ibrutinib with R-CHOP has since shown an ORR of 100%, with a CRR of 91% (n=22).[43] Bortezomib is another promising treatment that was combined with R-CHOP[44] and has led to three prospective randomised trials (NCT00931918, NCT01040871, and NCT01324596).

Lastly, a recent trial evaluated the effect of a sequential R-CHOP programme. After PET analysis of patient biopsies, participants then received R-CHOP for four doses followed by three doses of ifosfamide, carboplatin, and etoposide (ICE).[45] Among the first 200 patients, only 8 then had a transplant (personal communication). The LNH03 study then compared a cycle of rituximab and CHOP to rituximab combined with doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone (R-ACVBP) with sequential consolidation,[46] which demonstrated improved EFS for non-GC tumours only when using the R-ACVBP treatment.[47]

In conclusion, the advent of targeted agents may overcome the adverse impact of non-GC large cell lymphoma. Although these agents require further larger trials to be incorporated in existing guidelines and intensive chemotherapy may achieve similar results at lower cost, it is an exciting time for DLBCL treatment.

Table 2: Targeted therapy in DLBCL - dependence on cells of origin.

Target	Example agent	GCB	ABC
NF-κB	Bortezomib		+
PI_3K	Idelalisib		+
PKCβ	Enzastaurin		+
BTK	Ibrutinib		+
SYK	Fostamatinib		+
Multi-target/ angiogenesis	Lenalidomide	-/+	++
EZH_2	EZH_2 inhibitors	+	
BCL_2	$ABT-_{199}$	+	+

DLBCL: diffuse large B cell lymphoma; ABC: activated B cell lymphoma; GCB: germinal centre of B cell lymphomas.
From Andrew Zelenetz's presentation at this symposium.

Update on Current Trends in MCL Front-line Treatment

Professor Martin Dreyling

Diagnosis of MCL based upon pathology has been difficult due to the similarities with other types of cancer, which had previously led to an accurate identification of MCL cancers in only one-third of cases.[48] However, overexpression of cyclin D1 that is characteristic of MCL can now be used to confirm diagnosis, improving the accuracy to 98%. Once diagnosis is confirmed, risk factors should be assessed to optimise treatment. Hoster et al.[49] showed that patients with Ki-67 proliferative antigen levels >30% have significantly worse outcomes, even when treated with intensified treatment. Identification using a standardised method[50] and treatment of patients with high Ki-67 levels has therefore been included in the current European Society for Medical Oncology (ESMO) recommendations for MCL.[51] The Mantle Cell International Prognostic Index (MIPI) – an automatic web calculator that requires four parameters: performance status, age, elderly age, and leukocyte count – has been confirmed by the major study groups worldwide[51-54] and has been recommended for use in clinical routine as well as trials. Overall, within MCL, indolent cases have a prevalence of 10–15%, whilst 'classical' MCL accounts for 80% of cases, and 'transformed' types account for 5%.[55]

Current treatment recommendations include dose intensification (Figure 1), as a meta-analysis of randomised trials showed PFS and OS benefits.[55,56] Merli et al.[57] used cyclophosphamide, vincristine, doxorubicin, and dexamethasone treatment alternated with high-dose methotrexate and cytarabine treatment (HYPER-CVAD/MA); however, only one-third of patients completed the trial due to toxicity. A European trial with nearly 500 patients substituted the three cycles of R-CHOP with three cycles of rituximab with dexamethasone, cytarabine, cisplatin (R-DHAP) and found that molecular remission improved from 37% to 70%, as well as significant improvement of PFS.[58]

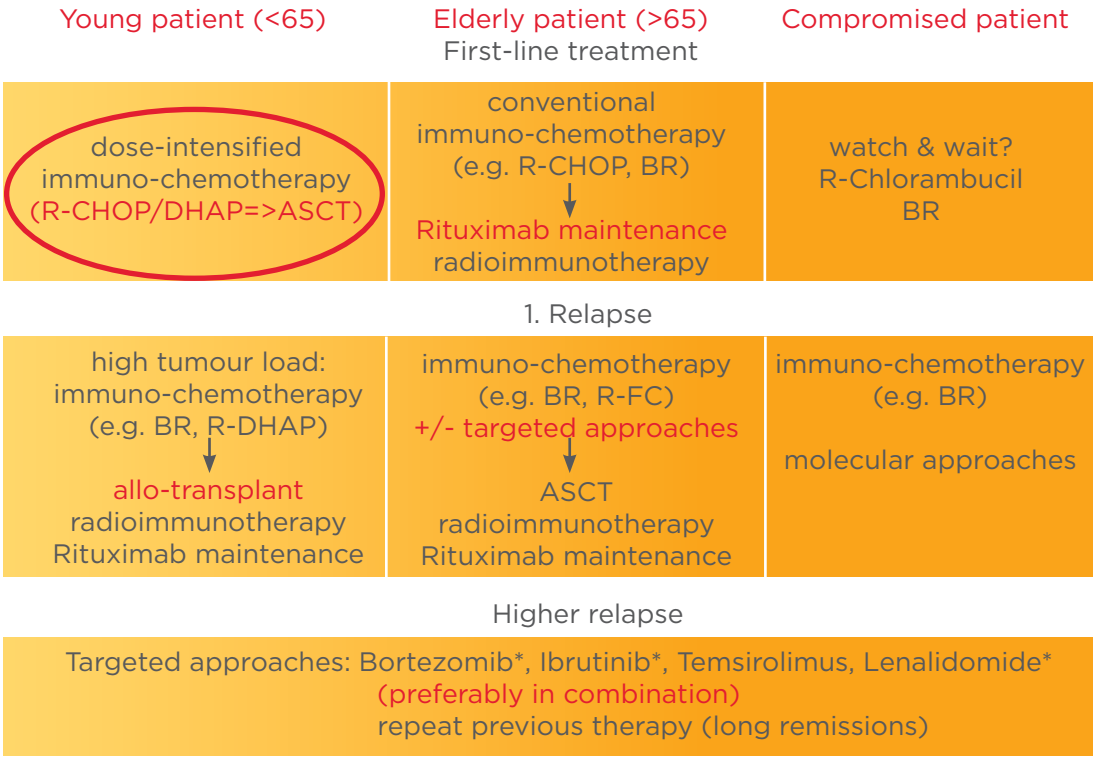

Figure 1: Treatment options for mantle cell lymphoma.
ASCT: autologous stem cell transplantation; BR: bendamustine and rituximab; DHAP: dexamethasone, cytarabine, and cisplatin; R-CHOP: rituximab + cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone; R-DHAP: rituximab + DHAP; R-FC: rituximab + fludarabine and cyclophosphamide.
From Martin Dreyling's presentation at this symposium.

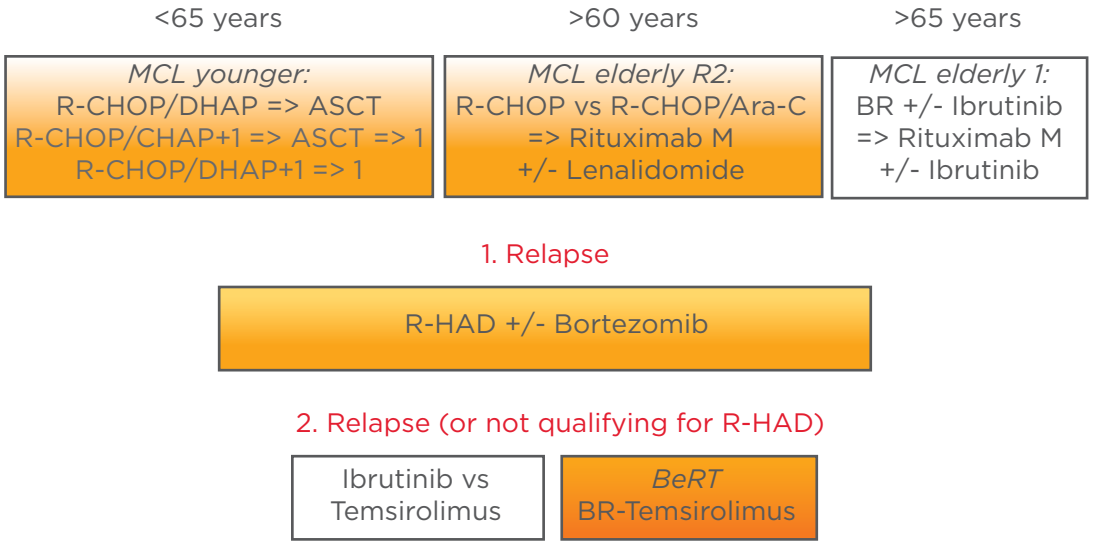

Figure 2: European Mantle Cell Lymphoma Network: Study generation 2014.
Ara-C: cytarabine; ASCT: autologous stem cell transplantation; BR: bendamustine and rituximab; DHAP: dexamethasone, cytarabine, and cisplatin; R-CHOP: rituximab + cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone; R-DHAP: rituximab + dexamethasone, cytarabine, and cisplatin; R-FC: rituximab + fludarabine and cyclophosphamide; R-HAD: rituximab, high-dose Ara-C, and dexamethasone.
Modified from European Mantle Cell Lymphoma Network.[76]

The treatment of elderly patients constitutes the majority of cases since the median age of disease is ~65 years.[55] A study performed in the 1960s that compared R-CHOP against bendamustine demonstrated the same OS across treatments,[59] suggesting that bendamustine should be evaluated with regard to its suitability in elderly patients as the only treatment given.[2] A study published in 2012 evaluated R-CHOP treatment followed by a maintenance period of either rituximab, IFN-α, or PEG-IFN for 2 months. Results showed that prolonged rituximab after R-CHOP significantly increased the remission duration ($p<0.0001$) and OS,[60] and has since been incorporated into national and international guidelines.

Regarding molecular targeted approaches, bortezomib, ibritumomab tiuxetan, temsirolimus, and lenalidomide have been registered for MCL in either the USA or Europe. There are studies combining bortezomib with R-CHOP, whilst a recent Phase I trial that combined temsirolimus with bendamustine and rituximab demonstrated a strong response rate and is currently being evaluated through a Phase II trial.[61]

Ruan et al.[62] explored an R-squared combination of rituximab and lenalidomide without any chemotherapy and reported an overall ongoing remission around 80%, with a CRR of 55%. Although it was a small study, this is undergoing a further large randomised study across eight European countries. Targeting of the B cell receptor pathway[63] with ibrutinib through BTK demonstrated high compliance, a complete response of 40%, and partial response of 37% in bortezomib-naïve patients (n=30) after a median of 14.7 months with very rare side-effects that included pneumonia, cellulitis, and Grade 4/5 sepsis.[64]

Whilst the first standard of care in younger patients is autologous stem cell transplantation, and in older patients it includes high-dose cytarabine during induction, recent promising clinical trials suggest that the first-line and second-line treatment options may soon be revised, as illustrated in Figure 2 from the European MCL Network.

Extending Treatment Possibilities in PTCL

Professor Bertrand Coiffier

As with DLBCL, PTCL shows a wide heterogeneity and there are currently several types of PTCLs, some of which are targetable with specific therapies. The OS of patients with PTCL is very poor and similar to that of angioimmunoblastic lymphoma.[65]

Current problems with PTCL include the rarity of the disease, causing the cancer types to be combined with other types of cancer when evaluated in clinical trials. Whilst the first-line therapy can be inadequate for many patients, the role of transplantation as first-line or for refractory diseases is not well defined either. As it is known that subtypes of PTCL respond differently, a universal first-line therapy would not be appropriate. For example, enteropathy-associated T cell lymphoma has very good results with autologous transplant as first-line therapy. There is only one randomised study that compared R-CHOP to etoposide, ifosfamide, cisplatin as an alternating treatment with doxorubicin, bleomycin, vinblastine (VIP-rABVD) in 88 patients and demonstrated that although VIP-rABVD therapy was not found to be superior to R-CHOP, around 40% of patients on R-CHOP showed EFS after around 30 months of treatment and 60% of patients therefore required alternative treatment.[66]

Novel investigative drugs for PTCL include brentuximab vedotin (SGN-35), mogamulizumab (anti-CCR4), and pralatrexate as first-line therapy, whilst, romidepsin, panobinostat, alisertib, and crizotinib have been evaluated in relapsing patients. Whilst pralatrexate resulted in a good response rate in one-third of patients and a median survival of 3.5 months, the duration of response was 10.1 months and there was some common toxicities such as mucositis, thrombocytopaenia, and neutropaenia that could render the drug unsuitable for combination with other treatments.[67] Romidepsin is a histone deacetylase inhibitor evaluated in three Phase II multicentre studies that included 150 PTCL patients, where it was reported that the majority of patients had reductions in the tumour volume from baseline.[68] Additional histone deacetylase inhibitors such as vorinostat, panobinostat, and belinostat are also under clinical development. Alisertib (MLN8237) is an investigational small oral aurora A kinase (AAK) inhibitor, undergoing a Phase III trial for relapsed or refractory PTCL.[69] Brentuximab vedotin is an antibody-drug conjugate that resulted in tumour reduction in 79% of patients[70] with relapsed T cell lymphomas, but requires further research due to the low patient numbers (n=29).

Most front-line therapies investigated are based upon CHOP. A Phase I study combined CHOP with romidepsin and reported a 1-year estimated PFS of 63.9% at a median follow-up of 10 months (n=27).[71] This front-line therapy study has progressed to Phase III, comparing CHOP with CHOP and romidepsin over 3–5 years, and plans to enrol 420 patients (NCT01796002). Focusing on the NK/T cell lymphoma subtype, L-asparaginase and methotrexate resulted in improved PFS in 19 relapsed or refractory patients.[72] The SMILE study comparing methotrexate and L-asparaginase + ifosfamide and etoposide demonstrated a 45% CRR, whilst toxicities included a high rate of Grade 4 neutropaenia (92%, n=38).[73,74]

There is another point of debate regarding the role and timing of autologous transplants. There are currently five Phase II retrospective trials in first-line consolidation, suggesting that the 5-year OS is 50%, whilst PFS is around 35-40%. It can be an option for some very aggressive subtypes, however, as yet there are no randomised trials so the true impact of autologous transplantation on survival is still unknown. Another retrospective study found that allogeneic compared to autologous transplants were associated with worse outcomes in nearly all cases due to toxicity.[75]

In conclusion, PTCL first-line therapy for many patients is currently inadequate and although there are promising results from new drugs in development, further trials are necessary to determine which treatments are most suitable for each PTCL subtype. Future combinations will probably be based upon CHOP, whereas the role of transplant for first-line therapy is uncertain but may be appropriate for relapsing patients such as those with DLBCL.

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