BRIDGING TO TRANSPLANT IN DIFFUSE LARGE B CELL LYMPHOMA

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ABSTRACT

Non-Hodgkin lymphoma (NHL) is the eighth most common malignancy worldwide. Diffuse large B cell lymphoma (DLBCL) is the most frequent subtype, accounting for >30% of NHL cases. Advances in novel approaches in the last two decades, such as immunotherapy with rituximab, have achieved improvements in terms of overall and long-term survival rates. The current standard of care for the first-line treatment of DLBCL is chemotherapy with rituximab plus cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisolone; this regimen achieves complete and sustained remission in approximately 60% of patients. Nevertheless, DLBCL relapses in 30–40% of patients, of which 10% develop refractory disease. Recent findings have demonstrated that substantial responses could be achieved after second or third-line treatments with combined chemotherapy. Since 2012, the aza-anthracenedione, pixantrone, has been approved as a single agent for relapsed or refractory DLBCL. The drug could be a new option as a bridging therapy to consolidate autologous or allogeneic stem cell transplantation, which in turn, can deliver prolonged durations of remission. Numerous clinical studies are ongoing that aim to improve salvage rates, outcomes, and access to stem cell transplantations for relapsed or refractory DLBCL. The development of novel targeted therapies or chemotherapeutics, such as pixantrone, will help to salvage more patients and achieve further sustained and complete responses without compromising their quality of life.

Keywords: Non-Hodgkin lymphoma (NHL), diffuse large B cell lymphoma (DLBCL), refractory DLBCL, relapsed DLBCL, salvage therapy, pixantrone, stem cell transplantation (SCT).

INTRODUCTION

Non-Hodgkin lymphoma (NHL) is the eighth most common malignancy worldwide,[1] with diffuse large B cell lymphoma (DLBCL) being its most frequent subtype. DLBCL accounts for over 30% of cases of NHL.[2] It is a rapidly growing and aggressive malignancy in which large B cells with high levels of mitotic activity spread into lymph nodes or other tissues outside the lymphatic system. DLBCL generally occurs in patients >50 years old, and is slightly more common in women.[3]

Over the last two decades, advances in novel therapeutic approaches, such as immunotherapy with rituximab, have achieved very good results in terms of overall and long-term survival.[4-6] The current standard of care for the first-line treatment of DLBCL is chemotherapy with rituximab plus cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisolone, yielding complete and sustained remission in ~60% of cases.[5]

Despite these good results, between 30% and 40% of patients relapse following first-line therapy and an additional 10% present the refractory disease.[6-8] As defined by the criteria of Cheson et al.,[9] relapsed DLBCL is characterised by the appearance of any new lesion after a complete response (CR), while refractory DLBCL is defined as failure of <50% of lesions to reduce in size following initial treatment. In these clinical settings, the standard therapeutic

option is to initiate high-dose therapy prior to either autologous or allogeneic stem cell transplantation (SCT). Patients who are ineligible for SCT or who fail after second-line therapy have a poor prognosis,[10] but recent findings have revealed that they could benefit from alternative salvage therapies.[11] Salvage therapies may also be used as a bridge to autologous or allogeneic SCT. The aim of this article is to provide an overview of advances and perspectives related to induction therapies as a bridge to transplantation in relapsed or refractory DLBCL (RR-DLBCL), as well as novel strategies in multiply relapsed DLBCL (MR-DLBCL).

MANAGEMENT OF RELAPSED OR REFRACTORY DIFFUSE LARGE B CELL LYMPHOMA

Management of Refractory Diffuse Large B Cell Lymphoma in Patients Eligible for Stem Cell Transplantation

Salvage chemotherapy as a bridge to autologous SCT is the standard therapeutic option for relapsed DLBCL and is successful in 30–40% of patients.[12] High-risk, chemotherapy-sensitive patients with a low probability of success with autologous SCT may be oriented to allogeneic SCT. Rates of relapse and progression in high-risk patients are comparable for the two approaches, although allogeneic SCT is associated with higher rates of non-relapse mortality than autologous SCT.[13,14]

There are many salvage therapies available, mostly involving rituximab in combination with standard antineoplastic agents. The most frequently used combinations are as follows:[15]

- R-ICE: rituximab plus ifosfamide, carboplatin, and etoposide
- R-DHAP: rituximab plus cytosine, arabinoside, cisplatin, and dexamethasone
- R-GDP: rituximab plus gemcitabine, dexamethasone, and cisplatin
- R-ESHAP: rituximab plus etoposide, methylprednisolone, cytarabine, and cisplatin
- R-GemOx: rituximab plus gemcitabine and oxaliplatin

What is the Best Salvage Therapy?

The best chemotherapy regimens are those that provide the highest response rates with the most tolerable toxicity. There is still no clear evidence regarding the superiority of one regimen over the other. Two prospective randomised studies have compared available salvage therapies (CORAL [COllaborative trial in Relapsed Aggressive Lymphoma] and LY12) but have failed to detect any significant differences in clinical outcomes, as detailed below.

COllaborative trial in Relapsed Aggressive Lymphoma (CORAL) Study

In the multicentre Phase III CORAL study, 477 patients with CD20+ DLBCL during their first relapse or who had disease that was refractory to first-line therapy were randomly allocated (1:1) to three courses of R-ICE (243 patients) or three courses of R-DHAP (234 patients). In both groups, treatment was followed by high-dose chemotherapy with carmustine, etoposide, cytarabine, and melphalan (BEAM), and then autologous SCT.[16,17] Response rates were 64% (95% confidence interval [CI]: 56–70%), and 63% (95% CI: 55–69%), respectively. Overall, 50% of patients were able to proceed to autologous SCT, mainly due to an insufficient response to the second-line therapy. There was no significant difference between the two rituximab (R-ICE and R-DHAP) regimens in terms of 3-year event-free survival (EFS) or overall survival (OS).

In the subpopulation that underwent autologous SCT, 122 patients received 1-year maintenance treatment with rituximab and 120 patients were assigned to observation only.[16] At 4 years, no difference in EFS was observed between the rituximab maintenance group and the control group (52% versus 53%, respectively), although there was a 15% attributable risk of serious adverse events in the active therapy group. Rituximab is therefore not recommended as a maintenance therapy after autologous SCT.

In the subpopulation that failed to proceed to autologous SCT, 13 patients died and 6 withdrew consent.[18] The remaining 203 patients were candidates for third-line chemotherapy, for which they had an overall response rate (ORR) of 39%, including 27% CR/unconfirmed complete response (CRu) and 12% partial response (PR) (Figure 1). Of these, 32% (n=64) of patients subsequently underwent autologous SCT (n=56) or allogeneic SCT (n=8). The authors concluded that, while third-line salvage chemotherapy for DLBCL can lead to a clinical response, with the chance for transplantation and long-term survival, the rates are still relatively low and there is an urgent need for new drugs.

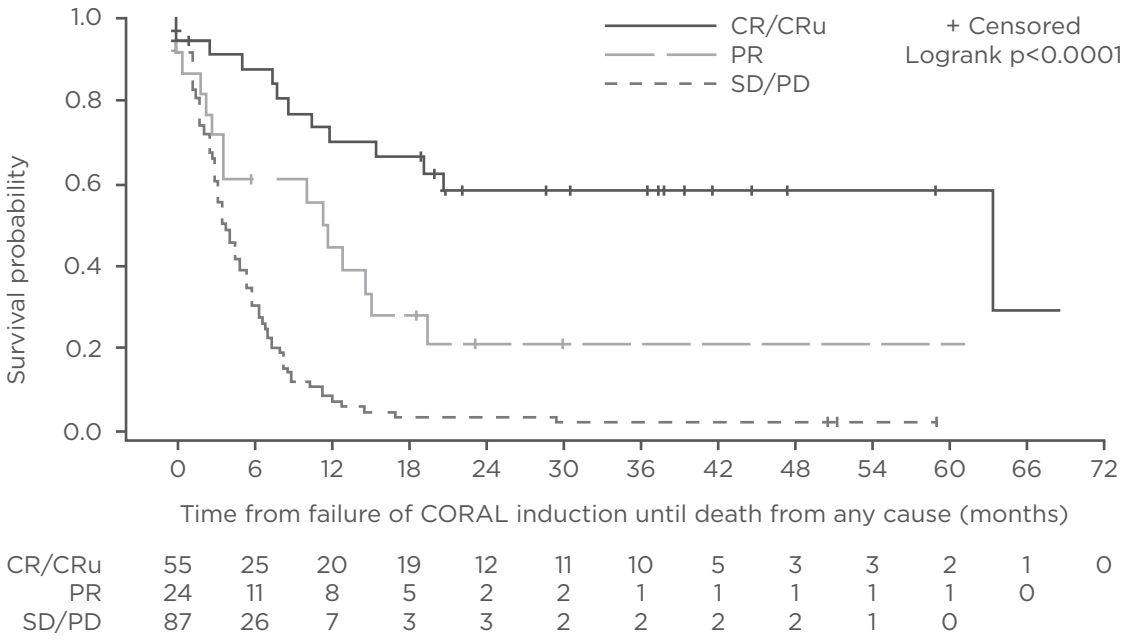

Figure 1: Overall survival (months) of 116 patients from time-to-treatment failure of CORAL induction according to the response to the third-line regimen.[18]

DLBCL: diffuse large B cell lymphoma; SD/PD: stable disease/progressive disease; PR: partial remission; CR: complete response; CRu: unconfirmed complete response; CORAL: COllaborative trial in Relapsed Aggressive Lymphoma study.

LY12 Study

The LY12 Phase III study was conducted by the National Cancer Institute of Canada in patients with RR-DLBCL. The aim was to compare two salvage therapies R-DHAP (n=310) and R-GDP (n=309),[19,20] followed by autologous SCT, which was performed in 49% and 52% of cases, respectively. Four-year survival rates were comparable, with EFS rates of 26% and 26%, and OS of 39% and 39%, respectively. Notably, patients in the R-GDP treatment arm seemed to benefit from lower toxicity and higher scores for quality of life.

Other Studies

Other agents are being explored as bridging therapies in RR-DLBCL. As an example, in an open-label Phase II study, the combination of everolimus (an mTOR inhibitor) and rituximab were evaluated in 24 heavily pre-treated patients with RR-DLBCL.[21] The ORR was 38% with three patients achieving CR and six patients with PR. Two of the patients with a CR were able to use this regimen as a bridging therapy and consequently underwent allogeneic SCT. After a follow-up period of 19 months, both patients were alive and disease-free.

Recently, the German High Grade Non-Hodgkin Lymphoma Study Group conducted a Phase II study in 84 patients with relapsed and refractory aggressive NHL to evaluate rituximab as an addition to graft-versus-host-disease prophylaxis following SCT.[22] After myeloablative conditioning, all patients underwent allogeneic SCT, after which they were randomly allocated to receive rituximab or placebo (1:1). The results demonstrated that the addition of rituximab did not affect the incidence of graft-versus-host-disease or OS.

Other authors have also explored the addition of a new monoclonal antibody to a chemotherapy regimen. For example, a multicentre Phase II trial investigated the safety and efficacy of the anti-CD^{20} monoclonal antibody, ofatumumab, combined with ICE or DHAP as a second-line therapy in 61 patients with B cell lymphomas, including RR-DLBCL.[23] The ORR was 61% for a CR of 37% (stem cell mobilisation was successful in 43 out of 45 patients). In the subsequent randomised comparison with rituximab, there was no difference between the two arms in terms of relative risk or progression-free survival (PFS).[24]

Can we Predict the Outcomes for Patients with Refractory Diffuse Large B Cell Lymphoma?

The poor outcomes obtained in patients with RR-DLBCL indicate that there remains a substantial

unmet medical need. A recent multi-cohort study, SCHOLAR-1 (Retrospective NHL Research) in patients with refractory DLBCL reported homogeneous outcomes with response rates of between 20% and 30% and a median OS of approximately 6 months.[25] Some prognostic factors have been identified for salvage therapy in RR-DLBCL. In the CORAL study, after BEAM and autologous SCT, 3-year EFS and OS were not significantly different but the outcomes were dependent on prior rituximab use, relapse within the first 12 months, and secondary age-adjusted International Prognostic Index (IPI) (Figure 1).[16] Poorer outcomes in patients with early relapse after autologous SCT (<12 months) are consistent with those of the PARMA trial and other earlier studies.[12,26,27]

As previously stated, rituximab-naïve patients from the CORAL study had higher response rates and 3-year EFS than patients previously exposed to rituximab (response rates: 83% versus 51%, p<0.001; and 3-year EFS, 47% versus 21%, p<0.001, respectively).[16] These results are in accordance with data from a retrospective study on R-ESHAP in patients with or without previous exposure to rituximab.[28] As many patients develop disease that is refractory to rituximab, the available evidence suggests that its role in salvage therapy should be reconsidered. This challenge should also be overcome by the development of new chemotherapy combinations and novel agents.[29] Finally, relapsed patients appear to have a higher OS than refractory patients.[30] A low-risk age-adjusted IPI at relapse was also associated with higher PFS and OS rates.[31]

Management of Refractory Diffuse Large B Cell Lymphoma in Patients Not Eligible for High-Dose Therapy and Autologous Stem Cell Transplantations

A substantial proportion of patients are not eligible for high-dose chemotherapy followed by autologous SCT. This may result from advanced age or comorbidities, as they are refractory to second-line treatment, or because they express a wish not to undergo the treatment. Patients who are ineligible for high-dose chemotherapy followed by autologous SCT as described in the bone marrow transplant guidelines have distinctly lower survival rates.[10,32,33] Treatment options comprise enrolment in Phase I or II clinical trials, palliative care with radiotherapy, rituximab therapy, and optimal supportive care.[34]

Management of Multiply Relapsed Diffuse Large B Cell Lymphoma

The standard of care for patients experiencing a second relapse is not clearly established and prognosis is extremely poor.[35] Third-line chemotherapy may be attempted in chemosensitive patients, with the objective of achieving sufficient response to initiate allogeneic SCT. Allogeneic SCT appears to be the main option in MR-DLBCL, in the event that a histocompatible donor is available for a patient. This option offers two main advantages, namely the infusion of tumour-free stem cells and the graft-versus-lymphoma effect.[36-38]

In a retrospective study of the GITMO (Gruppo Italiano Trapianto di Midollo Osseo) database, 165 patients who underwent autologous SCT relapsed and were subsequently treated with allogeneic SCT.[39] The results showed an ORR of 49%, with 43% of patients achieving CR and a further 5% obtaining PR. On the other hand, myeloablative conditioning with high-dose chemotherapy can generate higher transplant-related morbidity and non-relapse mortality. Thus, non-myeloablative or reduced-intensity conditioning approaches have been and continue to be evaluated.[40-44]

Chemotherapy can also be effective in MR-DLBCL. The CORAL study investigators conducted a retrospective analysis of patients failing second-line therapy (R-ICE or R-DHAP) and who could not proceed to autologous SCT (n=203).[11] Third-line therapy included ICE (19%), DHAP (18%), gemcitabine-containing (14%), and miscellaneous regimens (32%), with or without rituximab. ORRs were lower than those of second-line therapies in the intent-to-treat analysis (39% versus 63%), but still acted as a bridging therapy in 32% of patients who underwent high-dose chemotherapy followed by autologous SCT (n=56), or high-dose chemotherapy followed by allogeneic SCT (n=8). In this third-line setting all patients were ineligible for (allogeneic) SCT, and a non-negligible proportion of this cohort benefited from autologous SCT.

In the subgroup of patients who were able to undergo a transplant, the median OS was 11.1 months, with a 1-year OS of 42%, compared with a median OS of 3.3 months (1-year OS, 16%) in patients who did not undergo transplantation (p<0.0001). OS was influenced by secondary age-adjusted IPI at the point of failure.

Table 1: Overall survival according to prognostic factors.[18]

Parameter	n	Median OS (months)	Range (months)	1-year OS (%)	95% CI (lower–upper)	p-value
Total population	193	4.4	3.4–5.9	23.0	16.8–29.8	-
Tertiary IPI						
0–2	63	10.3	5.9–12.8	41.3	29.1–53.0	<0.0001
>2	52	3.2	2.6–4.2	6.4	1.7–15.7	-
Third-line immunotherapy						
Yes	56	5.6	3.4–10.6	33.2	20.3–46.7	0.42
No	116	5.4	3.4–6.9	21.3	13.7–30.0	-
Response to third-line regimen						
CR/CRu	55	63.6	15.5–NA	70.0	50.5–83.1	<0.0001
PR	24	11.7	2.6–15.2	44.4	22.2–64.6	-
SD/PD	87	3.7	3.2–5.0	8.3	3.6–15.3	-
Transplantation						
Yes	64	11.1	8.3–19.5	41.6	26.7–55.8	<0.0001
No	129	3.3	2.7–4.2	16.3	10.3–23.5	-
Transplantation type						
Autologous SCT	56	11.5	8.5–NA	43.1	26.9–58.3	0.37
Allogeneic SCT	8	7.9	1.3-NA	33.3	4.6–67.6	-

SCT: stem cell transplantation; CI: confidence interval; CRu: complete response undetermined; IPI: International Prognosis Index; NA: not available; OS: overall survival; SD/PD: stable disease/progressive disease; PR: partial remission.

However, the type of third-line regimen did not affect the outcomes, nor did the type of SCT (autologous or allogeneic). In a multivariate analysis, the IPI at relapse and SCT independently predicted OS (hazard ratio [HR]: 2.41 and 0.38, respectively) (Table 1).

Overall, it appears that prolonged remission can still be achieved in an acceptable proportion of MR-DLBCL patients, with effective salvage regimens acting as bridging therapies to enable SCT. However, an improvement in salvage rates is a crucial requirement that needs to be addressed; the development of novel therapeutic agents will improve outcomes that allow more patients to be treated with SCT.

Pixantrone in Multiply Relapsed B Cell Non-Hodgkin syndrome

Pixantrone dimaleate is a novel aza-anthracenedione with unique structural and physiochemical properties,[45,46] whose effects on DNA damage induction and cell death appear to be different from those of doxorubicin and anthracyclines. Pixantrone impairs mitotic fidelity, resulting in aberrant mitosis. The mechanism of action and efficacy of pixantrone seem to be independent of p53 status and influenced by checkpoint kinase 1 inhibition.[47-49]

The development of pixantrone was initiated to address severe cardiotoxicity issues related to the anthracyclines. As pixantrone lacks an iron-binding site, it has less potential to produce reactive oxygen species and does not form toxic drug-metal complexes. Pixantrone has also been demonstrated to be selective for Type II topoisomerase in stabilising enzyme-DNA complexes, which has also been hypothesised to explain the attenuated cardiotoxicity.[50] These advantages, along with less alcohol metabolite formation in cardiac tissue, account for the limited cardiac toxicity potential. Thus with pixantrone, there are no dose restrictions or warnings related to prior anthracycline use. However, as stated in the summary of product characteristics, patients with prior cumulative doses of doxorubicin or equivalent exceeding 450 mg/m^2 should receive careful risk versus benefit consideration before receiving treatment with pixantrone.[45]

Table 2: Response rates until the end of study in patients with aggressive B cell non-Hodgkin lymphoma receiving their third or fourth-line therapy.[53]

	Pixantrone	Comparator	p-value
Patients with aggressive B cell non-Hodgkin lymphoma with histology determined by central review (n=78)			
Number of patients	39	39	-
CR (%)	7 (17.9)	0 (0.0)	0.012
CR or CRu (%)	9 (23.1)	2 (5.1)	0.047
ORR (%)	17 (43.6)	5 (12.8)	0.005
Patients with aggressive B cell non-Hodgkin lymphoma with histology determined by central review who had previously received rituximab (n=38)			
Number of patients	20	18	-
CR or CRu (%)	6 (30.0)	1 (5.6)	0.093
ORR (%)	9 (45.0)	2 (11.1)	0.033

CR: complete response; CRu: unconfirmed complete response; ORR: overall response rate.
p-value versus comparator (Fisher's exact test).

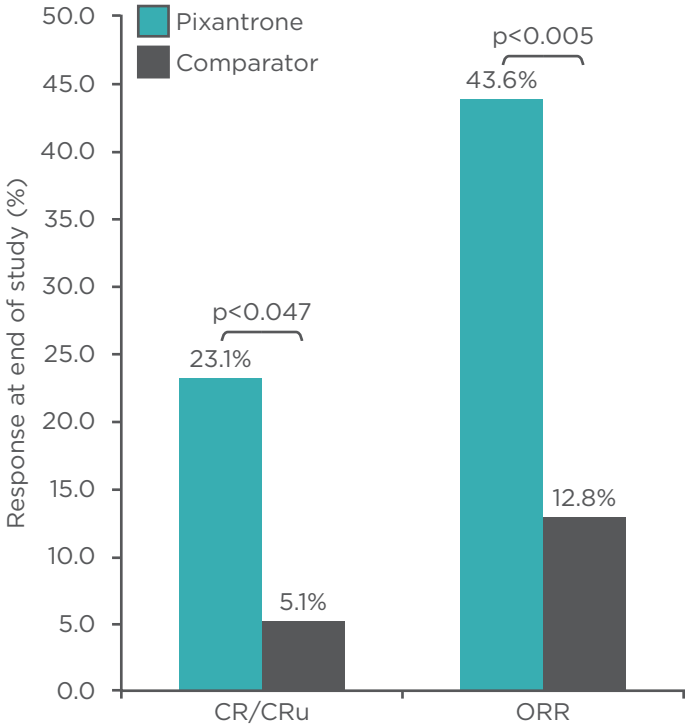

Figure 2: Post-hoc analysis: Response at end of study in patients with aggressive B cell non-Hodgkin lymphoma (determined by central review) receiving their third or fourth-line of therapy.[53]
CR: complete response; CRu: unconfirmed complete response; ORR: overall response rate.
p-value versus comparator (Fisher's exact test).

Pixantrone (Pixuvri®, CTI BioPharma Corp.) has a conditional European marketing approval for monotherapy in adults with RR or MR aggressive B cell NHL. This authorisation was based on the results of the Phase III PIX301 study. This open-label, randomised, controlled, multicentre, single-agent, Phase III trial evaluated the efficacy of pixantrone in the treatment of patients with relapsed, aggressive NHL after more than two combination chemotherapy regimens.[51,52] Pixantrone was therefore assessed in the setting of third-line therapy and beyond. A total of 140 patients were randomised (1:1) into two treatment arms: pixantrone (on Days 1, 8, and 15 of 28-day cycles) or a comparator (at the physician's discretion) for up to six cycles of treatment. The primary endpoint was independently assessed CR and CRu. Approximately half of the patients had previously received rituximab therapy.

In the intention-to-treat population, the primary endpoint CR/CRu rate at the end of study was 24.3% (median duration 9.6 months) and 7.1% (median duration 4.0 months) for the pixantrone and the comparator arm, respectively (p=0.009).[52] The ORR at the end of the study reached 37.1% versus 14.3% (p=0.001). Most importantly, pixantrone achieved CR/CRu in patients that had PR, stable disease, or progressive disease from prior intensive salvage therapies. Overall, 82% (14 out of 17) of the pixantrone CR/CRu had a suboptimal response to these prior therapies and yet went on to achieve a CR with pixantrone. Median PFS survival was longer in the pixantrone arm (5.3 months; 95% CI: 2.3–6.2) than in the comparator arm (2.6 months; 95% CI: 1.9–3.5;

p=0.005; HR: 0.6 [95% CI: 0.42–0.86]). Similar results were observed in the subpopulation of patients with DLBCL (4.6 months; 95% CI: 2.3–6.5 versus 2.1 months; 95% CI: 1.8–3.2; p<0.001; HR: 0.47 [95% CI: 0.30–0.71]).

In a *post hoc* analysis of the trial, the population with a histologically confirmed diagnosis after central review was subdivided according to previous rituximab use and whether they received the study treatment as a third or fourth-line.[53] In this population, when it was used in the third or fourth-line, pixantrone monotherapy was more effective than comparator in terms of response (CR: 23.1% versus 5.1%, p=0.047; ORR: 43.6% versus 12.8%, p=0.005; Table 2, Figure 2). These results were found to be consistent in patients who had previously received rituximab. Moreover, the observation of a 45.0% ORR with pixantrone in those patients versus 43.6% in the whole population (Table 2) suggests that treatment with pixantrone may have more potential as a bridge to transplant.

The most common Grade 3 or 4 adverse events for pixantrone in the entire study were cytopenias (uncomplicated, non-cumulative neutropenias, leukopenias, or thrombocytopenias), with an incidence of febrile neutropenias in 7.4% of cases for pixantrone versus 3.0% for comparator agents.[52] No high-grade treatment-emergent alopecia, mucosal inflammation, or opportunistic infections were reported for pixantrone and the incidence of severe infections was low.[45]

Following these promising results, a larger scale randomised, active-controlled, multicentre Phase III trial (PIX306 study) was initiated and is currently recruiting participants.[54,55] This trial aims to enrol 260 patients with RR B cell NHL or follicular Grade 3 lymphoma who previously received at least one rituximab-containing multi-agent therapy regimen and are not eligible for SCT. In the study protocol, patients are randomised (1:1) to pixantrone and rituximab combination or gemcitabine plus rituximab for up to six cycles of treatment. The primary endpoint is PFS; secondary endpoints comprise OS, CR rate, ORR, and safety outcomes.

The National Institute for Health and Care Excellence (NICE) published a final guidance document on February 26th 2014, on pixantrone monotherapy in RR or MR B cell NHL.[56] Key clinical evidence from PIX301 allowed NICE to appraise pixantrone under the single technology appraisal process, which concluded that the available results demonstrated that pixantrone can be a therapeutic option in RR or MR B cell NHL in the third or fourth-line settings. Cost-effectiveness assessments revealed that pixantrone was a cost-effective therapeutic option with an incremental cost-effectiveness ratio of £22,000 per quality-adjusted life year gained. Thus, pixantrone is currently licensed under the indications cited above; further clinical studies will evaluate its benefits in other therapeutic situations alone or in combination therapies.

IS PIXANTRONE A CANDIDATE FOR BRIDGING TO AUTOLOGOUS STEM CELL TRANSPLANTATION?

The trial evidence with pixantrone indicates that this agent can induce CR in patients with relapsed aggressive NHL.[52,53] Clinical responses have even been observed in patients with disease that was refractory to standard salvage chemotherapy. The response appears to be sufficiently strong to hypothesise that mobilisation of stem cells may be an option. Although this has not been demonstrated in the clinical trial setting, this finding implies that bridging to autologous SCT may be feasible with pixantrone and should be explored further.

FUTURE PERSPECTIVES AND CONCLUSION

Patients failing after second-line therapy for DLBCL suffer from an overall poor prognosis. Nevertheless, recent findings have demonstrated that substantial responses could be achieved after second or third-line treatments with combined chemotherapy. The novel agent, aza-anthracenedione pixantrone as a third-line approach or beyond, has demonstrated efficacy in the same patient setting. Thus, these therapies might be successfully used as a bridge to consolidation of autologous or allogeneic SCT, which in turn can deliver prolonged remission durations. Numerous clinical studies are being conducted to improve salvage rates and outcomes of RR-DLBCL. The development of novel chemotherapeutic agents or targeted therapies will certainly help to salvage more patients and achieve further sustained CRs without compromising the quality of life of the patient.

REFERENCES

1. International Agency for Research on Cancer, GLOBOCAN 2012: Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012, IARC, Lyon, France, 2013. Available at: http://globocan.iarc.fr/Pages/fact_sheets_population.aspx. Last accessed: 1 July 2016.

2. Jaffe ES et al. Classification of lymphoid neoplasms: The microscope as a tool for disease discovery. Blood. 2008; 112(12):4384-99.

3. Smith A et al. Incidence of haematological malignancy by sub-type: A report from the Haematological Malignancy Research Network. Br J Cancer. 2011;105(11):1684-92.

4. Matsuki E, Younes A. Checkpoint Inhibitors and other immune therapies for Hodgkin and non-Hodgkin lymphoma. Curr Treat Options Oncol. 2016;17(6):31.

5. Coleman M et al. Role of rituximab and rituximab biosimilars in diffuse large B-cell lymphoma. Clin Lymphoma Myeloma Leuk. 2016;16(4):175-81.

6. Coiffier B et al. Long-term outcome of patients in the LNH-98.5 trial, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: A study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood. Sep 23 2010;116(12):2040-5.

7. Pfreundschuh M et al. CHOP-like chemotherapy plus rituximab versus CHOP-like chemotherapy alone in young patients with good-prognosis diffuse large-B-cell lymphoma: a randomised controlled trial by the MabThera International Trial (MInT) Group. Lancet Oncol. 2006;7(5):379-91.

8. Habermann TM et al. Rituximab-CHOP versus CHOP alone or with maintenance rituximab in older patients with diffuse large B-cell lymphoma. J Clin Oncol. 2006; 24(19):3121-7.

9. Cheson BD et al. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007;25(5):579-86.

10. Feugier P et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. J Clin Oncol. 2005;23(18):4117-26.

11. Van Den Neste E et al. Diffuse Large B-Cell Lymphoma (DLBCL) Patients Failing Second-Line R-DHAP Or R-ICE Chemotherapy included In the Coral Study. Abstract 764. 55th ASH Annual Meeting and Exposition. 7–10 December 2013.

12. Philip T et al. Autologous bone marrow transplantation as compared with salvage chemotherapy in relapses of chemotherapy-sensitive non-Hodgkin's lymphoma. N Engl J Med. 1995;333(23): 1540-5.

13. Doocey RT et al. Allogeneic haematopoietic stem-cell transplantation for relapsed and refractory aggressive histology non-Hodgkin lymphoma. Br J Haematol. 2005;131(2):223-30.

14. Lazarus HM et al. A comparison of HLA-identical sibling allogeneic versus autologous transplantation for diffuse large B cell lymphoma: A report from the CIBMTR. Biol Blood Marrow Transplant. 2010;16(1):35-45.

15. Sehn LH, Gascoyne RD. Diffuse large B-cell lymphoma: optimizing outcome in the context of clinical and biologic heterogeneity. Blood. 2015;125:22-32.

16. Gisselbrecht C et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol. 28(27): 4184-90.

17. Gisselbrecht C et al. Rituximab maintenance therapy after autologous stem-cell transplantation in patients with relapsed CD20(+) diffuse large B-cell lymphoma: Final analysis of the collaborative trial in relapsed aggressive lymphoma. J Clin Oncol. 2012; 30(36):4462-9.

18. Van Den Neste E et al. Outcome of patients with relapsed diffuse large B-cell lymphoma who fail second-line salvage regimens in the International CORAL study. Bone Marrow Transplant. 2016; 51(1):51-7.

19. Crump M et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. J Clin Oncol. 2014;32(31): 3490-6.

20. Kuruvilla J et al. Salvage chemotherapy and autologous stem cell transplantation for transformed indolent lymphoma: a subset analysis of NCIC CTG LY12. Blood. 2015;126(6):733-8.

21. Barnes JA et al. Everolimus in combination with rituximab induces complete responses in heavily pretreated diffuse large B-cell lymphoma. Haematologica. 2013;98(4):615-9.

22. Glass B et al. Rituximab after lymphoma-directed conditioning and allogeneic stem-cell transplantation for relapsed and refractory aggressive non-Hodgkin lymphoma (DSHNHL R3): An open-label, randomised, Phase 2 trial. Lancet Oncol. 2014;15(7):757-66.

23. Matasar MJ et al. Ofatumumab in combination with ICE or DHAP chemotherapy in relapsed or refractory intermediate grade B-cell lymphoma. Blood. 2013;122(4):499-506.

24. van Imhoff GW et al. Ofatumumab versus rituximab salvage chemoimmunotherapy in relapsed or refractory diffuse large B-cell lymphoma: The Orcharrd Study (OMB110928). Abstract 630. 56th ASH Annual Meeting and Exposition. 6–9 December 2014.

25. Crump M et al. Outcomes in refractory aggressive diffuse large b-cell lymphoma (DLBCL): Results from the international SCHOLAR-1 study. Abstract 7516. ASCO Annual Meeting. 3–7 June 2016.

26. Vellenga E et al. Rituximab improves the treatment results of DHAP-VIM-DHAP and ASCT in relapsed/progressive aggressive CD20+ NHL: A prospective randomized HOVON trial. Blood. 2008; 111(2):537-43.

27. Guglielmi C et al. Time to relapse has prognostic value in patients with aggressive lymphoma enrolled onto the Parma trial. J Clin Oncol. 1998;16(10): 3264-9.

28. Martin A et al. R-ESHAP as salvage therapy for patients with relapsed or refractory diffuse large B-cell lymphoma: the influence of prior exposure to rituximab on outcome. A GEL/TAMO study. Haematologica. 2008;93(12): 1829-36.

29. Gisselbrecht C. Ofatumumab in diffuse large B cell lymphoma? Blood. 2013;122(4):469-70.

30. Kewalramani T et al. Rituximab and ICE as second-line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. Blood. 2004;103(10):3684-8.

31. Hamlin PA et al. Age-adjusted International Prognostic Index predicts autologous stem cell transplantation outcome for patients with relapsed or primary refractory diffuse large B-cell lymphoma. Blood. 2003;102(6):1989-96.

32. Thieblemont C, Coiffier B. Lymphoma in older patients. J Clin Oncol. 2007; 25(14):1916-23.

33. Jabbour E et al. Outcome of elderly patients with aggressive Non-Hodgkin's lymphoma refractory to or relapsing after first-line CHOP or CHOP-like chemotherapy: A low probability of cure. Leuk Lymphoma. 2004;45(7):1391-4.

34. Murthy V et al. Efficacy of palliative low-dose involved-field radiation therapy in advanced lymphoma: A phase II study. Clin Lymphoma Myeloma. 2008;8(4): 241-5.

35. Vose JM et al. Progressive disease

after high-dose therapy and autologous transplantation for lymphoid malignancy: clinical course and patient follow-up. Blood. 1992;80(8):2142-8.

36. Rezvani AR et al. Non-myeloablative allogeneic haematopoietic cell transplantation for relapsed diffuse large B-cell lymphoma: A multicentre experience. Br J Haematol. 2008;143(3): 395-403.

37. van Besien KW et al. Management of lymphoma recurrence after allogeneic transplantation: the relevance of graft-versus-lymphoma effect. Bone marrow transplantation. Bone Marrow Transplant. 1997;19(10):977-82.

38. Bishop MR et al. Clinical evidence of a graft-versus-lymphoma effect against relapsed diffuse large B-cell lymphoma after allogeneic hematopoietic stem-cell transplantation. Ann Oncol. 2008; 19(11):1935-40.

39. Rigacci L et al. Allogeneic hematopoietic stem cell transplantation in patients with diffuse large B cell lymphoma relapsed after autologous stem cell transplantation: A GITMO study. Ann Hematol. 2012 Jun;91(6):931-9.

40. Sirvent A et al. Low nonrelapse mortality and prolonged long-term survival after reduced-intensity allogeneic stem cell transplantation for relapsed or refractory diffuse large B cell lymphoma: Report of the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire. Biol Blood Marrow Transplant. 2010;16(1): 78-85.

41. Thomson KJ et al. Favorable long-term survival after reduced-intensity allogeneic transplantation for multiple-relapse aggressive non-Hodgkin's lymphoma. J Clin Oncol. 2009;27(3):426-32.

42. van Kampen RJ et al. Allogeneic stem-cell transplantation as salvage therapy for patients with diffuse large B-cell non-Hodgkin's lymphoma relapsing after an autologous stem-cell transplantation: An analysis of the European Group for Blood and Marrow Transplantation Registry. J Clin Oncol. 2011;29(10):1342-8.

43. Bacher U et al. Conditioning regimens for allotransplants for diffuse large B-cell lymphoma: Myeloablative or reduced intensity? Blood. 2012;120(20):4256-62.

44. Hamadani M et al. Impact of pretransplantation conditioning regimens on outcomes of allogeneic transplantation for chemotherapy-unresponsive diffuse large B cell lymphoma and grade III follicular lymphoma. Biol Blood Marrow Transplant. 2013;19(5):746-53.

45. European Medicines Agency. Pixuvri - Summary of Product Characteristics. 2013. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002055/WC500127968.pdf. Last accessed: 1 July 2016.

46. Adnan N et al. DNA binding by pixantrone. Org Biomol Chem. 2010; 8(23):5359-66.

47. Beeharry N et al. Pixantrone induces cell death through mitotic perturbations and subsequent aberrant cell divisions. Cancer Biol Ther. 2015;16(9):1397-406.

48. Pettengell R, Kaur J. Pixantrone dimaleate for treating non-Hodgkin's lymphoma. Expert Opinion on Orphan Drugs. 2015;3(6):747-57.

49. Results presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, October 2013, Boston.

50. Hasinoff BB et al. Cellular mechanisms of the cytotoxicity of the anticancer drug elesclomol and its complex with Cu(II). Biochem Pharmacol. 2015;93(3):266-76.

51. Engert A et al. EXTEND PIX301: A phase III randomized trial of pixantrone versus other chemotherapeutic agents as third-line monotherapy in patients with relapsed, aggressive non-Hodgkin's lymphoma. Clin Lymphoma Myeloma. 2006;7(2):152-4.

52. Pettengell R et al. Pixantrone dimaleate versus other chemotherapeutic agents as a single-agent salvage treatment in patients with relapsed or refractory aggressive non-Hodgkin lymphoma: A phase 3, multicentre, open-label, randomised trial. Lancet Oncol. 2012;13(7):696-706.

53. Pettengell R et al. Monotherapy with pixantrone in histologically confirmed relapsed or refractory aggressive B-cell non-Hodgkin lymphoma: Post-hoc analyses from a phase III trial. Br J Haematol. 2016. [Epub ahead of print].

54. U.S. National Institutes of Health. Comparison of Pixantrone + Rituximab with Gemcitabine + Rituximab in Patients with Aggressive B-cell Non-Hodgkin Lymphoma or Follicular Grade 3 Lymphoma Who Have Relapsed After Therapy and Are Not Eligible for Stem Cell Transplant (PIX-R). NCT01321541. Available at: http://clinicaltrials.gov/ct2/show/NCT01321541.

55. Belada D et al. Pixantrone-rituximab versus gemcitabine-rituximab in relapsed/refractory aggressive non-Hodgkin lymphoma. Future Oncol. 2016 [Epub ahead of print].

56. National Institute for Health and Care Excellence Technology appraisal guidance TA306. Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma. Available at: https://www.nice.org.uk/Guidance/ta306. Last accessed: 1 July 2016.