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Pixantrone, etoposide, bendamustine, rituximab (P[R]EBEN) as an effective salvage regimen for relapsed/refractory aggressive non-Hodgkin lymphoma—Polish Lymphoma Research Group real-life analysis

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ABSTRACT

Background: Despite a significant improvement in treatment outcomes, 30–40% of aggressive non-Hodgkin lymphomas (NHL) patients are refractory or relapse after the first line therapy. Half of them are not eligible to autologous stem cell transplantation (ASCT) due to failure of platinum-based salvage regimens. Pixantrone is conditionally approved in Europe in patients with R/R aggressive NHL failing at least 2 previous lines of therapy. Polish Lymphoma Research Group (PLRG) evaluated the efficacy and tolerability of P[R]EBEN combining pixantrone, etoposide, bendamustine with or without rituximab), a new regimen developed recently by Francesco d'Amore, in real-life experience.

Methods: In this retrospective audit, we analyzed the data of consecutive 25 R/R NHL cases, treated with P[R]EBEN regimen in 9 PLRG centers. Safety and efficacy data, including adverse reactions (AE), response rates, progression-free and overall survival (PFS and OS) were collected.

Results: Overall response rate (ORR) to P[R]EBEN regimen was 68% (40% CR and 28% PR). Most patients responded, relatively early, by second cycle of therapy. P[R]EBEN was effective in 8 out of 15 patients (53%) refractory to previous platinum-based salvage regimens. In 4 patients (16%) stabilization of disease (SD) during therapy was observed and further 4 patients (16%) progressed during the treatment (PD). Response rates were higher in patients, chemosensitive to their prior regimen (ORR – 87.5%, including 50% CR). At the median follow-up of 7.5 months (range 1–16) the median PFS and OS were not reached. Projected PFS and OS at 12 months are 68% and 78% respectively. The P[R]EBEN regimen was well tolerated and most of patients received it as out-patients. AEs grade $\geq$3 occurred in 17 patients (68%). Most common grade 3–4 AEs were due to hematological toxicity with febrile neutropenia observed in 5 patients (20%). There were no episodes of septic deaths. Six patients (24%) died during treatment and follow-up period, all of them due to lymphoma progression.

Conclusion: Our data suggest good efficiency and tolerability of P[R]EBEN regimen as a rescue therapy in patients with R/R aggressive NHL.

Abbreviations: AE, adverse event; Allo-SCT, allogeneic stem-cell transplantation; ASCT, autologous stem-cell transplantation; ASH, American Society of Hematology; CHOP, doxorubicin, cyclophosphamide, vincristine and prednisone; CR, complete response; CTCAE, common terminology criteria for adverse events; DLBCL, diffuse large B-cell lymphoma; G-CSF, granulocyte colony-stimulating factor; GvL, graft versus lymphoma; HDC, high dose chemotherapy; HGBL, high grade B-cell lymphoma; MCL, mantle cell lymphoma; NHL, non-Hodgkin lymphoma; ORR, overall response rate; OS, overall survival; PD, progressive disease; PET-CT, positron emission tomography combined with computed tomography; PFS, progression-free survival; PLRG, Polish Lymphoma Research Group; PR, partial response; P[R]EBEN, pixantrone, etoposide, bendamustine +/-rituximab; PTCL, peripheral T-cell lymphoma; RIC, reduced intensity conditioning; R/R, relapsed/refractory; SD, stable disease; TIN, transformed indolent lymphoma.

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Introduction

Introducing rituximab combined with anthracycline-based regimens as a standard first-line therapy in all eligible patients with aggressive non-Hodgkin lymphomas (NHL) resulted in significant improvement of their outcome. However, 30–40% of patients are still refractory to therapy or subsequently relapse [1–3]. In fit patients, salvage platinum-based regimens are recommended as a second-line therapy. Despite many attempts, none of the particular regimens is clearly superior [4–8]. Subsequent consolidation with high-dose chemotherapy (HDC) and autologous stem-cell transplantation (ASCT) has curative potential only in patients with chemo-sensitive disease. Half of relapse and refractory (R/R) patients are not eligible to HDC/ASCT due to the failure of salvage therapy, therefore alternative, more effective salvage regimens are needed [9,10].

Anthracyclines play the key role in the first line management of aggressive NHL, however, dose-related cumulative cardiotoxicity, have restricted their potential usage in rescue setting [11–14]. Pixantrone dimaleate (pixantrone), a new aza-anthracenadione was synthetized to reduce anthracycline-related cardiotoxicity, while maintaining their high therapeutic activity [11,15]. Although pixantrone chemical structure is similar to anthracyclines it neither generates reactive oxygen species nor forms alcohol metabolites responsible for drug-related cardiotoxicity and may be used in R/R settings [11]. It is conditionally approved as monotherapy in European Union countries in adult patients with R/R aggressive NHL failing at least 2 previous lines of therapy [16]. In the pivotal phase 3 study Pettengell et al. reported an overall response rate (ORR)/complete response (CR) of 37%/20% in relapsed aggressive NHL patients treated with pixantrone as at least third-line therapy. To increase the efficacy of pixantrone monotherapy it's combinations with monoclonal antibodies and other cytostatics have been studied [17–20].

The P[R]EBEN protocol (Pixantrone, [Rituximab], Etoposide, Bendamustine) developed by Francesco d'Amore, was the first regimen combining aza-anthracenadione and bendamustine. In the first promising clinical experience with P[R]EBEN in 30 patients with multiply R/R aggressive NHL Clausen et al. showed an ORR of 50% including 27% of complete metabolic responses [17,18]. Phase 1–2 study (NCT02678299) in R/R aggressive NHL is ongoing with estimated completion date in June 2019. As the Polish Lymphoma Research Group (PLRG) we present the results of the retrospective audit evaluating the efficacy and tolerability of this regimen in 25 patients with R/R NHL.

Patients and methods

In this retrospective analysis, we collected data of 25 R/R NHL patients treated with P[R]EBEN in 9 PLRG centers, in 2017–2018. The diagnosis according to the World Health Organization 2008 classification, was based on histopathological assessment of tissue samples excised before the 1st line therapy or – in transformed indolent lymphoma patients – after transformation [21].

The P[R]EBEN schedule consisted of pixantrone (50 mg/m^2 *iv* infused on days 1 and 8), etoposide (100 mg *iv* on day 1), bendamustine (90 mg *iv* on day 1) with the addition of rituximab (375 mg/m^2 *iv* on day 1) in patients with CD20 positive NHL. If feasible, each cycle was given in 21-days intervals for a maximum of 6 cycles [17,18].

Efficacy data including ORR, CR rate, progression-free survival (PFS) and overall survival (OS) as well as the safety data were collected. All patients were assessed for response with 18F-fluorocholine positron emission tomography combined with computed tomography (PET-CT), before therapy, after 2 cycles and 3 weeks after treatment completion. CR and PR were defined according to 2014 Lugano classification [22,23]. Eligible patients with objective response to the treatment were considered for consolidation with either HDT/ASCT or allogeneic hematopoietic stem-cell transplantation (allo-SCT) according to the local policy. Supportive treatment was administered as required according to the local standards, including adequate fluid intake and allopurinol for tumor lysis syndrome prevention, and granulocyte colony-stimulating factor (G-CSF) support as neutropenic fever (FN) prophylaxis. Adverse events (AEs) were classified according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Informed consent was obtained for experimentation with human subjects.

Statistical analyses

To characterize the study group and response to therapy we used descriptive statistical methods. Survival analysis was performed by Kaplan-Meier method; both PFS and OS were calculated from the time P(R)EBEN therapy was initiated to time of progression, death from any cause or the date of the last follow-up. Statistical analyses were performed using the software Statistica, version 10 (StatSoft, Krakow, Poland).

Results

Between January 2017 and July 2018, 25 consecutive heavily-pretreated patients with R/R NHL were treated according to the P[R]EBEN schedule in 9 Polish centers. Their median age was 51 years (range 26–74) with a male/female ratio of 2.57. The most common histologic subtype was diffuse large B-cell lymphoma (DLBCL, n = 15), followed by transformed B-cell indolent lymphoma subtypes (TIN, n = 7) and peripheral T-cell lymphoma (PTCL, n = 3). All patients had intermediate or high risk international prognostic index (IPI) prior to the start of salvage therapy. All patients received (R)-CHOP as initial induction therapy or after transformation to an aggressive lymphoma subtype. The majority of the patients (17/25; 68%) had primary refractory disease, most of primary refractory patients had failed also platinum-based salvage regimens (15/17; 88%). A further 8 (32%) were treated in relapse, including 4 after previous ASCT. Patients characteristics and demographics are summarized in Table 1.

All consecutive patients with DLBCL, TIN and PTCL who received at least 1 cycle of treatment with P[R]EBEN were included in the analysis. The median number of P[R]EBEN cycles received was 4 (range 3–6) with no dose reductions or dose delays. The overall response rate (ORR) at the end of treatment was 68% with a CR rate of 40% and PR rate of 28% (Table 2). The P[R]EBEN regimen was effective in 8 of 15 (53%) patients refractory to both first-line as well as platinum-based salvage regimens. Most responses were observed early, after second cycle, median 2 (range 1–3). In 4 patients stabilization of disease was observed (16% SD), 4 patients progressed during treatment (16% PD). Of the patients who achieved a CR, two were refractory to first line R-CHOP. In the 8 patients who achieved a CR or PR to their last regimen, the ORR was 87.5% with a 50% CRR.

At the median follow-up of 7.5 months (range 1–16), the median PFS and OS were not reached. Projected PFS and OS at 12 months are 68% and 78% respectively (Figs. 1 and 2). There were no significant differences in PFS and OS depending on the lymphoma subtype. After completion of P[R]EBEN salvage treatment, 6 patients (24%) proceeded to ASCT (3 DLBCL cases, 2 PTCL and 1 TIN). Post ASCT 5 patients were in metabolic CR and 1 in PR. Further 3 patients (12%) with TIN received a reduced intensity conditioning (RIC) allo-SCT. Post allo-SCT 2 patients were in metabolic CR and 1

Table 1
Baseline patient and disease characteristics.

Patient Demographics	
Male, n (%)	18 (72)
Female, n (%)	7 (28)
Median age, years (range)	51 (26–74)
≥ 60 years, n (%)	8 (32)
Median number of prior treatments, n (range)	3 (1–5)
Histologic type	
DLBCL	15 (60)
Transformed B-cell indolent lymphoma (TIN)	7 (28)
PTCL	3 (12)
ECOG Performance status n (%)	
0-1	19 (76)
≥ 2	6 (24)
Stage, n (%)	
I	0 (0)
II	6 (24)
III	1 (4)
IV	18 (72)
Bulky disease, n (%)	14 (56)
Median IPI, number (range)	4 (3–5)
Duration of last remission	
≥ 12 months, n (%)	6 (24)
<12 months, n (%)	19 (76)
Disease status	
Primary refractory, n (%)	17 (68)
Relapsed, n (%)	8 (32)
Refractory to salvage platinum-based regimens, n (%)	15 (60)
ASCT before PREBEN, n (%)	4 (16)

in PR. All of the patients after SCT were alive and their remission status did not change at the time of analysis. Six patients (24%) have died during the treatment or follow-up period due to lymphoma progression (2 with SD, 4 with PD after P[R]EBEN completion).

The treatment schedule was well tolerated and most patients received the second and further cycles as out-patients. In the analyzed group, AEs of all grade assessed according to Common Terminology Criteria for Adverse Events (CTCAE) occurred in 23 patients (92%), grade 3–4 AEs were observed in 17 patients (68%) with hematological toxicities being the most common. Grade 3 neutropenia was recorded in 10 patients (40%) while a single patient experienced grade 4 neutropenia (4%). Grade 3–4 neutropenias completely resolved after G-CSF administration, febrile neutropenia was noted in 5 patients (20%) but there were no episodes of septic death. Grade 3 anemia occurred in 6 patients (24%) and grade 3 thrombocytopenia in 5 patients (20%). Patients with grade 3 anemia or thrombocytopenia were supported with red blood cells or platelets transfusion. Infections were the most common non-hematological AEs, followed by polyneuropathy in 2 patients (8%). Grade 3 infections occurred in 8 patients (32%), including 5 patients (20%) with febrile neutropenia. Only 5 patients (20%) required additional hospitalization due to AEs, all with febrile neutropenia. There were no clinically significant cardiovascular events during treatment or follow-up. In 12 patients (48%), who underwent echocardiographic analysis at the end of treatment (all presented with more than one cardiological risk factor), we did not observe any left ventricle diastolic nor systolic dysfunction. The details of AEs are summarized in Table 3.

Discussion

Achieving a successful outcome to the treatment of refractory/relapsed aggressive NHL patients is still a challenge. Therefore, after the feasibility study results of P[R]EBEN were presented at the ASH and ICML conferences by d'Amore and Clausen we have offered this regimen as an alternative salvage regimen in PLRG hematology/oncology centers [17,18]. In the d'Amore study, the P[R]EBEN regimen was found not to be suitable for the treatment of other aggressive subtypes such as high-grade B-cell lymphoma (HGBCL) and mantle cell lymphoma (MCL), therefore patients with the above diagnoses were not included in the analysis [17,18]. Our retrospective audit confirmed the high overall response rate of 68% and metabolic CR rate in heavily pretreated relapsing/ refractory aggressive NHL patients observed in the published D'Amore data [17,18]. A complete metabolic response rate of 40% compares favorably to traditional second line platinum-based salvage regimens [4–8,24], and is almost double the CR rate of pixantrone monotherapy (PIX301 trial) and similar to previously described in P[R]EBEN studies designed by d'Amore and Clausen [16,25]. Comparable results were also reported by Hayman et al. in a phase I study in R/R B-cell NHL, where pixantrone was combined with bendamustine and rituximab [20]. What is more, in our group the response to P[R]EBEN was achieved in 64.6% of patients with the disease primary refractory to the therapy, 68.4% of patients with the response to the previous therapy lasting ≤12 months and 53.4% of the patients refractory to previous classical cisplatin based salvage therapies. All the situations mentioned above, are an unmet medical need, so whenever possible, such patients should be offered therapy with novel agents in clinical trials.

The results achieved with P[R]EBEN in this study are exceptionally good considering the extremely poor prognosis of R/R aggressive NHL patients. In multicohort, international, retrospective NHL study SCHOLAR-1, the objective response rate to the next therapy in the primary refractory patients was only 26% with median OS of 6.3 months [26]. In the CORAL study, the primary refractory patients, or those with early relapse (≤12 months) were reported to have a median overall survival of only 3.3 and 6.4 months respectively and the response to the third-line therapy in the patients failing second-line salvage regimens was 39% [10]. According to the other reports, less than 1 in 10 relapsing patients not responding to the first salvage regimen, survived 3 years [27,28]. In our patients treated with P[R]EBEN, the projected one-year PFS and OS were 68% and 78% respectively that warrants further investigation of this regimen.

An important aspect of our study is successful consolidation with ASCT or allo-SCT in 6/25 (24%) and 3/25 (12%) of the patients respectively. In the SCHOLAR-1 study, transplant procedures significantly prolonged median OS of refractory DLBCL [26]. Appio et al. described R/R patients treated with pixantrone monotherapy who received ASCT [29] and our data suggest further improvement of its efficacy by the combination strategy. Allo-SCT, due to the graft-versus lymphoma (GvL) effect, further reduces the probability of disease relapse and it is considered potentially curative in the patients with chemosensitive disease after ASCT failure. In our cohort, 3 patients with transformed indolent lymphomas underwent RIC allo-SCT without any transplant-related deaths observed. Malaspina et al. have recently reported a response to pixantrone in multiple relapsed DLBCL patient after failing allo-SCT [30].

In the context of durable responses and good tolerance observed in our analysis, P[R]EBEN should also be considered as a valuable therapeutic option for patients who do not qualify for ASCT due to their poor performance status, comorbidities or older age. In our group response was achieved in 4 out of 8 patients (50%) aged ≥60 years, with a safety profile comparable to the whole group. Recently published post-hoc analysis of PIX301 trial demonstrated durable responses and long-term remission after pixantrone monotherapy in some patients regardless the clinical response to the last regimen [16,25].

P[R]EBEN regimen was not only effective, but also safe and well tolerated in this heavily pretreated patient population, failing 1–5

Table 2
Response to PREBEN according to pretreatment parameters.

Parameter	Number of patients	Complete response n (%)	Partial response n (%)	Stable or progressive disease n (%)
All group	25	10 (40)	7 (28)	8 (32)
Age ≥ 60 years	8	2 (25)	2 (25)	4 (50)
Lymphoma subtype				
DLBCL	15	5 (33.3)	4 (26.7)	6 (40)
TIN	7	3 (42.9)	3 (42.9)	1 (14.2)
PTCL	3	2 (66.7)	0 (0)	1 (33.3)
DOR of the last treatment				
≥ 12 months	6	2 (33.3)	2 (33.3)	2 (33.3)
<12 months	19	8 (42.1)	5 (26.3)	6 (31.6)
Disease status				
Primary refractory	17	6 (35.2)	4 (23.5)	7 (41.1)
Refractory to salvage platinum-based regimens	15	4 (26.7)	4 (26.7)	7 (46.6)
Relapsed	8	4 (50)	3 (37.5)	1 (12.5)
Relapsed after ASCT	4	1 (25)	2 (50)	1 (25)

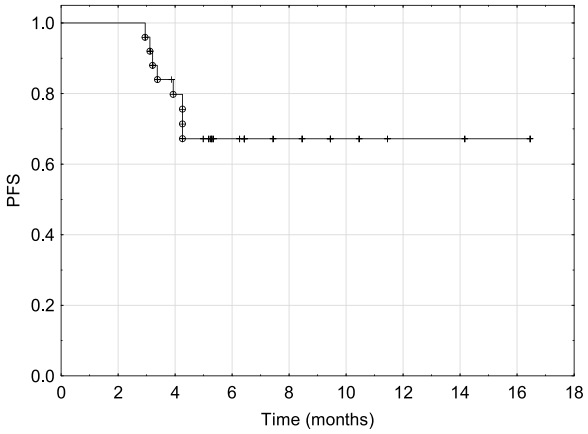

Fig. 1. PFS analysis of all patients.

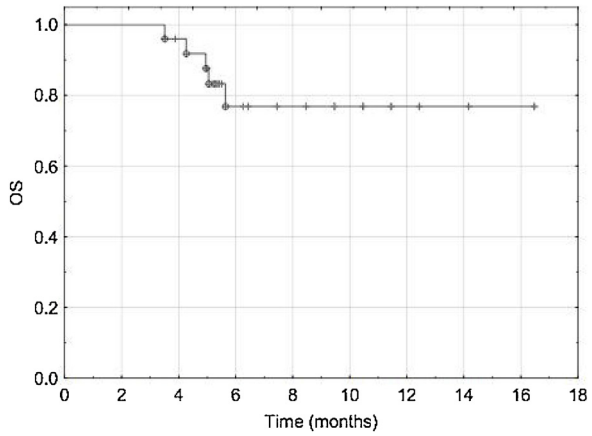

Fig. 2. OS analysis of all patients.

previous lines of treatment, including HDC/ASCT. In our audit and the study by d'Amore, Clausen et al. [17,18] the P[R]EBEN regimen toxicity was limited, predictable and manageable enabling the treatment to be delivered in an outpatient setting. In our series, patients were admitted to the hospital only for the first couple of days of the first cycle. There were no septic deaths during treatment and follow-up period. This rate was comparable to the one reported in the pivotal PIX301 study [25], suggesting no significant additional toxicity associated with P[R]EBEN as multi-drug regimen. Serious infections were reported in 32% of the patients, but they were manageable with empiric antibiotics in all cases. We did not observe any cardiotoxicity associated with P[R] EBEN regimen that confirms previous observations on the cardiac safety of pixantrone in NHL patients treated previously with anthracycline-containing protocols [16,25].

The limitations of this study are: retrospective character of the analysis, the small number of patients with different types of aggressive lymphoma and the short follow-up period. Our results confirmed that P[R]EBEN is feasible, effective and safe salvage regimen in R/R NHL in a real–life setting. It may not only be used as potential bridging to HDT/ASCT or allo-SCT in younger, fit patients, but also is an effective, well tolerated salvage regimen in elderly patients with comorbidities, where traditional, platinum-based chemotherapy protocols are too toxic. It's promising efficacy and manageable toxicity profile warrant further studies in larger patient group with longer follow-up. We all wait for the results of a proper prospective clinical trial, designed by Francesco d'Amore, currently on-going in aggressive R/R NHL.

Table 3
Adverse events, according to CTCAE ver 4.03.

Adverse events	All grade n (%)	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)
Neutropenia	23 (92)	6 (24)	6 (24)	10 (40)	1(4)
Anemia	21 (84)	8 (60)	7(28)	6 (24)	0
Thrombocytopenia	20 (80)	7 (28)	8 (60)	5 (20)	0
Polyneuropathy	2 (8)	0	0	2 (8)	0
Infection	8 (32)	0	0	8 (32)	0
Febrile neutropenia	5 (20)	0	0	5 (20)	0

Authorship statement

The authors had full access to the data and take full responsibility for its integrity. All authors have read and agreed with the content of the manuscript as written.

Conflict of interest

Monika Długosz-Danecka and Wojciech Jurczak declares research funding from Servier. Wojciech Jurczak declares participation in Servier advisory boards. Iwona Hus, Bartosz Puła, Artur Jurczyszyn, Tomasz Chojnacki, Beata-Blajer Olszewska, Joanna Drozd-Sokołowska, Małgorzata Raźny, Joanna Romejko-Jarosińska i Michał Taszner declare no conflict of interest.

CRediT authorship contribution statement

Monika Długosz-Danecka: Conceptualization, Data curation, Formal analysis, Project administration, Methodology, Writing - original draft, Writing - review & editing. **Iwona Hus**: Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing. **Bartosz Puła**: Formal analysis, Writing - review & editing. **Artur Jurczyszyn**: Formal analysis, Writing - review & editing. **Tomasz Chojnacki**: Data curation, Formal analysis, Writing - review & editing. **Beata Blajer-Olszewska**: Formal analysis, Writing - review & editing. **Joanna Drozd-Sokołowska**: Formal analysis, Writing - review & editing. **Małgorzata Raźny**: Formal analysis, Writing - review & editing. **Joanna Romejko-Jarosińska**: Formal analysis, Writing - review & editing. **Michał Taszner**: Formal analysis, Writing - review & editing. **Wojciech Jurczak**: Conceptualization, Data curation, Formal analysis, Project administration, Methodology, Supervision, Writing - original draft, Writing - review & editing.

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References

[1] Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002;346(4):235–42.
[2] Sehn LH, Donaldson J, Chhanabhai M, Fitzgerald C, Gill K, Klasa R, et al. Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. J Clin Oncol 2005;23(22):5027–33.
[3] Coiffier B, Thieblemont C, Van Den Neste E, Lepeu G, Plantier I, Castaigne S, 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 2010;116(12):2040–5.
[4] Philip T, Guglielmi C, Hagenbeek A, Somers R, Van der Lelie H, Bron D, 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.
[5] Appelbaum FR. Hematopoietic cell transplantation for non-Hodgkin's lymphoma: yesterday, today, and tomorrow. J Clin Oncol 2008;26 (18):2927–9.
[6] Moskowitz CH, Bertino JR, Glassman JR, Hedrick EE, Hunte S, Coady-Lyons N, et al. Ifosfamide, carboplatin, and etoposide: a highly effective cytoreduction and peripheral-blood progenitor-cell mobilization regimen for transplant-eligible patients with non-Hodgkin's lymphoma. J Clin Oncol 1999;17 (12):3776–85.
[7] Gisselbrecht C, Glass B, Mounier N, Singh Gill D, Linch DC, Trneny M, et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol 2010;28(27):4184–90.
[8] Smith SM, Burns LJ, van Besien K, Lerademacher J, He W, Fenske TS, et al. Hematopoietic cell transplantation for systemic mature T-cell non-Hodgkin lymphoma. J Clin Oncol 2013;31(25):3100–9.
[9] Feugier P, Van Hoof A, Sebban C, Solal-Celigny P, Bouabdallah R, Ferme C, 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.
[10] Van Den Neste E, Schmitz N, Mounier N, Gill D, Linch D, Trneny M, 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.
[11] Mordente A, Meucci E, Silvestrini A, Martorana GE, Giardina B. New developments in anthracycline-induced cardiotoxicity. Curr Med Chem 2009;16(13):1656–72.
[12] Krapcho AP, Maresch MJ, Hacker MP, Menta E, Oliva A, Giuliani FC, et al. Aza and diaza bioisosteric anthracene-9,10-diones as antitumor agents. Acta Biochim Pol 1995;42(4):427–32.
[13] Singal PK, Iliskovic N. Doxorubicin-induced cardiomyopathy. N Engl J Med 1998;339(13):900–5.
[14] Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer 2003;97 (11):2869–79.
[15] Mordente A, Meucci E, Martorana GE, Giardina B, Minotti G. Human heart cytosolic reductases and anthracycline cardiotoxicity. IUBMB Life 2001;52(1–2):83–8.
[16] Pettengell R, Coiffier B, Egorov A, Singer J, Sivcheva L. Long-term response and remission with pixantrone in patients with relapsed or refractory aggressive non-Hodgkin lymphoma: post-hoc analysis of the multicenter, open-label, randomized PIX301 trial. Clin Drug Investig 2018;38(6):527–33.
[17] Clausen M, Leppa S, Brown P, Goerloev J, Panny M, Willenbacher W, et al. The combination of pixantrone, etoposide, bendamustine and, in CD20+ tumors, rituximab (PREBEN) shows promising feasibility/efficacy in heavily pre-treated aggressive lymphomas of B- and T-cell phenotype – results of the pre-trial experience leading to a nordic phase 1/2 study (the PREBEN trial). Blood 2016;128(22) 1782-1782.
[18] d'Amore F, Leppä S, Larsen TS, Brown P, Relander T, Mannisto S, et al. A phase 1/2 study of pixantrone, etoposide, bendamustine and, in CD20+ tumors, rituximab in patients with relapsed aggressive B- or T-cell lymphomas- the P[R]EBEN study. Hematol Oncol 2017;35(S2):423–4.
[19] Belada D, Georgiev P, Dakhil S, Inhorn LF, Andorsky D, Beck JT, et al. Pixantrone-rituximab versus gemcitabine-rituximab in relapsed/refractory aggressive non-Hodgkin lymphoma. Future Oncol 2016;12(15):1759–68.
[20] Heyman B, Rizzieri D, Adams DJ, De Castro C, Diehl L, Li Z, et al. Phase I study of the combination of bendamustine, rituximab, and pixantrone in patients with relapsed/refractory B-cell non-Hodgkin lymphoma. Clin Lymphoma Myeloma Leuk 2018;18(10):679–86.
[21] Campo E, Swerdlow SH, Harris NL, Pileri S, Stein H, Jaffe ES. The 2008 WHO classification of lymphoid neoplasms and beyond: evolving concepts and practical applications. Blood 2011;117(19):5019–32.
[22] Cheson BD, Fisher RI, Barrington SF, Cavalli F, Schwartz LH, Zucca E, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32(27):3059–68.
[23] Van Heertum RL, Scarimbolo R, Wolodzko JG, Klencke B, Messmann R, Tunc F, et al. Lugano 2014 criteria for assessing FDG-PET/CT in lymphoma: an operational approach for clinical trials. Drug Des Devel Ther 2017; (11):1719–1728.
[24] Gisselbrecht C, Van Den Neste E. How I manage patients with relapsed/refractory diffuse large B cell lymphoma. Br J Haematol 2018;182(5):633–43.
[25] Pettengell R, Coiffier B, Narayanan G, de Mendoza FH, Digumarti R, Gomez H, 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.
[26] Crump M, Neelapu SS, Farooq U, Van Den Neste E, Kuruvilla J, Westin J, et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood 2017;130(16):1800–8.
[27] Ardeshna KM, Kakouros N, Qian W, Powell MG, Saini N, D'Sa S, et al. Conventional second-line salvage chemotherapy regimens are not warranted in patients with malignant lymphomas who have progressive disease after first-line salvage therapy regimens. Br J Haematol 2005;130(3):363–72.
[28] Elstrom RL, Martin P, Ostrow K, Barrientos J, Chadburn A, Furman R, et al. Response to second-line therapy defines the potential for cure in patients with recurrent diffuse large B-cell lymphoma: implications for the development of novel therapeutic strategies. Clin Lymphoma Myeloma Leuk 2010;10 (3):192–196.
[29] Appio L, Landoni C, La Targia M, Bertolli V, Chiarucci M, Crovetti G, et al. Single-agent pixantrone as a bridge to autologous stem cell transplantation in a patient with refractory diffuse large B-cell lymphoma. Chemotherapy 2017;62 (3):187–91.
[30] Malaspina F, Pellegrini C, Casadei B, Argnani L, Zinzani PL. Impressive response to pixantrone after allogeneic transplant in a multiple relapsed diffuse large B-cell lymphoma. Acta Haematol 2017;137(4):191–4.