SPOTLIGHT REVIEW ARTICLE

Spotlight on polatuzumab vedotin: new standards for diffuse large B-cell lymphoma?

Paola Ghione[1,2] and Gilles Salles[1,2]

[1]Lymphoma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center and [2]Weill Cornell Medical College, New York, NY, USA

Correspondence: G. Salles
sallesg@mskcc.org

Received: February 6, 2024.
Accepted: May 17, 2024.
Early view: May 30, 2024.

https://doi.org/10.3324/haematol.2022.282362

Abstract

Despite continuous improvements in the management and treatment of diffuse large B-cell lymphoma (DLBCL), approximately 35% of affected patients experience relapse or are refractory to frontline chemotherapy. For these patients, outcomes are far from satisfactory, and a real unmet need exists both to improve frontline treatment and to create better options for relapsed/refractory disease. Polatuzumab vedotin is an anti-CD79b antibody conjugated to the monomethyl auristatin E microtubule inhibitor. The molecule has recently been under the spotlight for the promising results of the frontline combination with rituximab, cyclophosphamide, doxorubicin and prednisone in the phase III POLARIX study, demonstrating improved progression-free survival over standard rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone. Remarkable improvements in terms of complete response rate and overall survival have also been achieved with polatuzumab vedotin by combining the antibody with the standard rituximab and bendamustine regimen for relapsed/refractory patients. Based on the results of these studies, health authorities in several countries granted approval for polatuzumab vedotin to be used as treatment both for patients with previously untreated DLBCL and for those with relapsed/refractory DLBCL. In this review, we summarize the data of major studies recently concluded with polatuzumab vedotin, and we provide an overview of the ongoing combination trials for frontline and relapsed/refractory DLBCL, outlining reported toxicities.

Introduction

Diffuse large B-cell lymphoma (DLBCL) is the most frequently diagnosed lymphoma. The cure rates of DLBCL have improved significantly with the introduction of the anti-CD20 antibody rituximab combined with the standard cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy.[1,2] Unfortunately, up to 40% of the patients experience lymphoma relapse or are refractory to frontline therapy, and had an estimated survival of 6 to 12 months in the era before chimeric antigen receptor (CAR) T-cell therapy.[3] In this context, treatments are rapidly evolving, with CAR T-cell therapy approved in the second line for DLBCL that is refractory to or relapses within a year from the end of first-line treatment, and with the introduction of bispecific antibodies. Despite these progresses, about half of patients still experience disease progression after having received CAR T-cell therapy or an autologous stem cell transplant (performed when DLBCL recurrence occurs after 1 year). For those unable to access this form of treatment, approximately 80% will die of progressive lymphoma or complications of subsequent lines of therapy.[4,5] Furthermore, several studies have demonstrated the biological heterogeneity of DLBCL and, using gene profiling (cell of origin classification) or genetic alterations, subgroups with distinct outcomes that could potentially benefit from targeted therapeutic interventions have been identified.[3]

Based on these data, several trials have been conducted to improve the effect of rituximab plus CHOP (R-CHOP). Some approaches aimed at reforming the schedule or dose or substituting some of the compounds (CHOP every 14 days,[6] R-ACVBP [rituximab plus doxorubicin, cyclophosphamide, vindesine, bleomycin, prednisone],[7] R-DA-EPOCH [rituximab plus dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin],[5] CHOP, and obinutuzumab instead of rituximab [G-CHOP]),[8] others at adding a new targeted drug (lenalidomide,[9] ibrutinib,[10]

bortezomib,[11] azacytidine[12]) or including maintenance with rituximab,[13,14] lenalidomide[15] or enzastaurin.[16] However, despite thousands of patients enrolled, no real upgrade in the standard of care was achieved.[3]

Polatuzumab vedotin is an anti-CD79b antibody, conjugated with monomethyl auristatin E, a microtubule inhibitor.[17,18] The class of antibody-drug conjugates allows the delivery of a cytotoxic agent to cells carrying a specific target: this mechanism aims at increasing the potency of the compound to the neoplastic cells and reducing the toxicity to normal tissues. The target protein of polatuzumab vedotin, CD79b, is part of the complex of the B-cell receptor, involved in signal transmission, and is expressed on the surface of mature B-cell lymphomas, including more than 95% of all DLBCL.[17,19]

Polatuzumab vedotin has shown promising activity in relapsed/refractory B-cell lymphoma as a single agent[20] and in combination with the anti-CD20 antibody rituximab,[21] with 23/42 patients (55%) achieving a response to the single agent.[20] In a cohort of 39 patients with relapsed or refractory DBCL receiving the combination of polatuzumab-rituximab, 21 of them (54%) achieved an objective response, including eight (21%) with a complete response.[21] The most common grade 3-4 toxicities encountered with the single agent were neutropenia (40%), anemia (11%) and peripheral sensory neuropathy (9%); the most common grade 3-4 toxicities with polatuzumab-rituximab were neutropenia (23%), anemia (8%), and diarrhea (8%).[21]

Polatuzumab in combination with bendamustine-rituximab (BR)[22] elicited a significantly higher overall response rate and more prolonged overall survival compared with BR alone (median overall survival 12.4 *vs*. 4.7 months, hazard ratio [HR]=0.42; 95% confidence interval [95% CI]: 0.24-0.75, *P*=0.002) in a randomized phase II trial of patients with relapsed or refractory DLBCL who had received at least two prior lines of therapy.[22] For this last indication, despite the limited size of the study, polatuzumab vedotin combined with BR was approved by health authorities worldwide in 2019 for DLBCL patients having failed previous therapies. Finally, a large phase III randomized trial of frontline treatment of DLBCL tested a modified regimen of R-CHOP replacing vincristine with polatuzumab vedotin (pola-R-CHP) *versus* the classic R-CHOP.[23] The study detected a meaningful improvement in the progression-free survival of patients treated with pola-R-CHP compared to those treated with R-CHOP and a reduction in the risk of progression, relapse, or death after a median follow-up of 28.2 months (HR=0.73, 95% CI: 0.57-0.95; *P*=0.02).[23,24] This study led to the approval of the pola-R-CHP combination for previously untreated DLBCL in several countries since 2022.

In this review, we expand on the use of polatuzumab vedotin in DLBCL, describe the results of the trials that have been recently concluded, and the preliminary data of the ongoing ones, with a focus on efficacy and toxicity.

Polatuzumab vedotin for untreated diffuse large B-cell lymphoma

Pola-R-CHP (POLARIX)

A phase IB/II trial in frontline DLBCL exploring the safety and overall response rate of the combination of polatuzumab vedotin and rituximab, cyclophosphamide, doxorubicin, and prednisone (pola-R-CHP), excluding vincristine from the classic CHOP regimen to avoid cumulative neurological toxicity from polatuzumab. The study demonstrated an encouraging overall response rate of 89%, with a complete response rate of 77%.[25] On these premises, a phase III randomized study called POLARIX was conducted, comparing pola-R-CHP with standard R-CHOP, and was published in early 2022.[23] POLARIX was a phase III randomized 1:1 double-blinded and placebo-controlled study: the primary endpoint was progression-free survival and secondary endpoints were overall survival and safety. The study enrolled 879 patients from 23 countries, of whom 440 received pola-R-CHP and 439 classic R-CHOP. Eligibility criteria allowed the enrollment of patients with higher risk DLBCL (International Prognostic Index [IPI] score of 2 or more) regardless of cell of origin or rearrangement status of *MYC*, *BCL2*, and *BCL6*. It has been established that high-grade B-cell lymphoma, formerly defined as DLBCL with translocation of combinations of *MYC* with *BCL2* or *BCL6* (double- or triple-hit lymphomas) is a form of large B-cell lymphoma with particularly aggressive features.[26] Transformed lymphoma from indolent histology and primary mediastinal and central nervous system involvement were excluded. The schema of the pola-R-CHP regimen is detailed in Table 1. Of note, the study required use of granulocyte colony-stimulating factor as neutropenia prophylaxis for all six cycles of chemotherapy. Response to the treatment was assessed with positron emission tomography/computed tomography as per the Lugano criteria.[27]

At a median follow-up of 28.2 months, the primary endpoint (progression-free survival) was met, with the hazard ratio for progression, relapse, or death being lower in the pola-R-CHP group than in the R-CHOP group (HR=0.73, 95% CI: 0.57-0.95; *P*=0.02). Treatment with pola-R-CHP significantly improved the progression-free survival rate at 2 years (76.7%, 95% CI: 72.7-80.8) compared to that achieved with the standard R-CHOP regimen (70.2%, 95% CI: 65.8-74.6). Among the secondary endpoints, event-free survival was better in the pola-R-CHP group than in the R-CHOP group (2-year event-free survival: 75.6% [95% CI: 71.5-79.7] and 69.4% [95% CI: 65.0-73.8%], respectively). Complete response rate and overall survival did not differ significantly between patients in the pola-R-CHP and R-CHOP arms. However, patients who achieved a complete response with pola-R-CHP were more likely to achieve a persistent remission than those receiving R-CHOP (HR for relapse or death=0.70, 95% CI: 0.5-0.98). With a median follow-up of more than 3 years (39.7 months), the initial

Table 1. Polatuzumab vedotin studies and treatment schemas used.

Schema	N of cycles	Doses and schedules	Frequency
Schemas for previously untreated diffuse large B-cell lymphoma			
Pola-R-CHP	6 + 2 infusions of rituximab	Polatuzumab vedotin 1.8 mg/kg IV day 1 Rituximab 375 mg/m^2 IV day 1* Cyclophosphamide 750 mg/m^2 IV day 1 Doxorubicin 50 mg/m^2 IV day 1 Prednisone 100 mg/die P.O. days 1-5	Every 21 days
Pola-DA-EPCH-R	6	Polatuzumab vedotin 1.8 mg/kg IV day 1 Rituximab 375 mg/m^2 IV day 1* Etoposide 50 mg/m^2/die CIV days 1-4 (96 h) Cyclophosphamide 750 mg/m^2/die IV day 5 Doxorubicin 10 mg/m^2/die CIV days 1-4 (96 h) Prednisone 60 mg/m^2/bid P.O. days 1-5	Every 21 days
Pola-mini-R-CHP	6	Polatuzumab vedotin 1.8 mg/kg IV day 1 Rituximab 375 mg/m^2 IV day 1*, 1,400 mg SC cycles 2-6 Cyclophosphamide 400 mg/m^2 IV day 1 Doxorubicin 25 mg/m^2 IV day 1 Prednisone 40 mg/m^2 P.O. days 1-5 (round up to nearest 25 mg)	Every 21 days
Schemas for relapsed/refractory diffuse large B-cell lymphoma			
Pola-BR	Up to 6	Polatuzumab vedotin 1.8 mg/kg IV day 1 Rituximab 375 mg/m^2 IV day 1* Bendamustine 90 mg/m^2 IV days 1 and 2	Every 21 days
Pola-R-GemOx	Up to 8	Polatuzumab vedotin 1.8 mg/kg IV day 1 Rituximab 375 mg/m^2 IV day 1* Gemcitabine 1,000 mg/m^2 IV day 2 Oxaliplatin 100 mg/m^2 IV day 2	Every 21 days
Pola-R-ICE	3 up to 4	Polatuzumab vedotin 1.8 mg/kg IV day 1 Rituximab 375 mg/m^2 IV day 1* Etoposide 100 mg/m^2 IV days 1-3 Carboplatin AUC 5 max 800 mg IV day 2 Ifosfamide 5,000 mg/m^2 IV (24 h) day 2	Every 21 days
Pola-mosunetuzumab	Up to 6	Polatuzumab vedotin 1.8 mg/kg IV day 1 Mosunetuzumab SC days 1, 8, and 15 (cycle 1), then day 1 only	Every 21 days

*Rituximab given alone separately a day before day 1 of cycle 1. IV: intravenous; P.O.: *per os*; CIV: continuous intravenous infusion; AUC: area under the curve; SC: subcutaneous.

difference in progression-free survival between the two arms was sustained (HR=0.76, 95% CI: 0.60-0.97).[28]

The safety profile in the pola-R-CHP group was similar to that in the R-CHOP group (Table 2). The most common grade 3-4 adverse events were neutropenia (28% in the pola-R-CHP group and 30.8% in the R-CHOP group), febrile neutropenia (13.8% and 8%, respectively), and anemia (12% and 8%, respectively). Despite pola-R-CHP inducing more febrile neutropenia, the incidence of grade 3-4 infections was similar in the two groups (15.2% in the pola-R-CHP group and 12.6% in the R-CHOP group).

Of interest, the incidence and severity of peripheral neuropathy were superimposable in the pola-R-CHP arm and the standard R-CHOP arm, with rare (<2%) grade 3-4 events in both arms. In this regard, 4.4% of the patients reduced the dose of polatuzumab vedotin, and 8% reduced the dose of vincristine because of peripheral neuropathy. Overall, dose reductions related to adverse events occurred in 9.2% of the patients receiving pola-R-CHP and in 13% of patients receiving R-CHOP.

Adverse events resulting in death occurred in 13 patients in the pola-R-CHP group and ten patients in the R-CHOP group and were mainly pneumonia (7 patients) and sepsis (4 patients).

Efficacy of pola-R-CHP in diffuse large B-cell lymphoma subgroups

The POLARIX study was not powered to look at progression-free survival in subgroups of DLBCL. However, these analyses showed some trends suggesting distinct benefits of pola-R-CHP in different populations. For instance, a difference in 2-year progression-free survival of 10% or more favoring pola-R-CHP was observed in patients with an IPI score equal to or greater than 3, in those without bulky disease, and those with a tumor with an “activated B-cell” phenotype (assessed using gene expression profiling) or displaying overexpression of Myc and Bcl2 proteins. Reciprocally, patients younger than 60 years, with germinal center DLBCL, bulky disease, and low-intermediate IPI score did not appear to benefit from pola-R-CHP. It should be noted here that the Hans algorithm based on immunohistochemistry is widely used in clinical practice to evaluate the cell of origin, but this

Table 2. Toxicity profiles (reported toxicities with a frequency of >20% overall) of pola-R-CHP compared with R-CHOP and pola-BR compared with BR.

Adverse events	Pola-R-CHP		R-CHOP	
	Grade 1-2 %	Grade 3-4 %	Grade 1-2 %	Grade 3-4 %
Peripheral neuropathy	52.9	1.6	53.9	1.1
Nausea	41.6	1.1	36.8	0.5
Neutropenia	30.8	28.3	32.6	30.8
Diarrhea	30.8	3.9	20.1	1.8
Anemia	28.7	12.0	26.0	8.4
Adverse events	**Pola-BR**		**BR**	
	Grade 1-2 %	Grade 3-4 %	Grade 1-2 %	Grade 3-4 %
Anemia	53.8	28.2	25.6	17.9
Neutropenia	53.8	46.2	38.5	33.3
Thrombocytopenia	48.7	41.0	28.2	23.1
Peripheral neuropathy	43.6	0	7.7	0
Diarrhea	38.5	2.6	28.2	2.6
Fatigue	35.9	2.6	35.9	2.6
Pyrexia	33.3	2.6	23.1	0
Nausea	30.8	0	41.0	0
Decreased appetite	25.6	2.6	20.5	0

Pola-R-CHP: polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, prednisone; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; Pola-BR: polatuzumab vedotin, bendamustine, rituximab; BR: bendamustine, rituximab.

approach is less precise than RNA gene expression profiling assays (such as the commercial digital assay "Nanostring"), which will reclassify about 20% of the cases identified by immunohistochemistry.

This prompted *post hoc* exploratory analyses of DLBCL molecular subtypes determined from patients' samples from the POLARIX study to refine the knowledge on the efficacy of pola-R-CHP beyond the cell of origin. The analysis was performed using the mutation-based LymphGen algorithm[29] and the dark zone signature (including patients with double- and triple-hit lymphoma)[30] using RNA-sequencing data. While underpowered, the preliminary results suggested that pola-R-CHP benefited DLBCL patients usually considered to have a poorer outcome with R-CHOP. These included patients whose tumors are characterized as EZB (with *EZH2* mutations/*BCL2* translocations) and MCD (*MYD88/CD79B*-mutated) LymphGen subgroups and cases in which the genetic subgroup could not be determined. A tendency towards lower 2-year progression-free survival with pola-R-CHP was observed in patients with *BCL6* fusions and *NOTCH2* mutations (BN2). Finally, patients with a dark-zone signature who had an adverse prognosis when receiving R-CHOP appeared to have a better outcome when they received pola-R-CHP.[31]

These results underline the biological heterogeneity of DLBCL, which, besides clinical characteristics such as bulk or IPI score, is not routinely captured with widely available methodologies. The rationale for a distinct activity of polatuzumab vedotin in biological subsets is not yet known.

Ongoing trials

Pola-DA-EPCH-R

A single-center phase II trial[32] is exploring the addition of polatuzumab vedotin to dose-adjusted etoposide, cyclophosphamide, doxorubicin, and rituximab (pola-DA-EPCH-R) (NCT04231877). Like the POLARIX schema, vincristine (administered as a continuous infusion in this regimen) is being substituted by polatuzumab. This trial is enrolling aggressive lymphomas for which DA-EPOCH-R can be considered standard treatment, such as high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and gray zone lymphoma. Polatuzumab vedotin is administered at the standard dose of 1.8 mg/kg on the first day of treatment and, unlike the rest of the chemotherapy in the regimen, its dose is not adjusted. The preliminary data for 18 patients enrolled in the study have been published recently[32] and revealed that the study had met its primary safety endpoint for the combination. For patients evaluable at end of treatment response, the overall response rate was 94% with 76% complete responses. Major grade 3-4 adverse events included neutropenia (94%), thrombocytopenia (56%), anemia (39%), oral mucositis (22%), thromboembolic events (22%), febrile neutropenia (17%), hyperglycemia (17%), abdominal pain (11%) and hypokalemia (11%). Peripheral neuropathy was common (44%) but not higher than grade 1. Further data are warranted to evaluate this combination's efficacy and toxicity profile.

Pola-R-mini-CHP (POLAR BEAR)

This is a randomized multicenter phase III trial promoted by

the Nordic Lymphoma Group (NCT 04332822). It is comparing treatment with R-mini-CHOP and R-mini-CHP with polatuzumab vedotin in older patients with DLBCL.[24] The study is enrolling 200 participants who are either 80 years or older or over 75 years old and established to be frail, according to the simplified comprehensive geriatric assessment. Besides DLBCL, the study is also enrolling patients with follicular lymphoma grade 3b, primary mediastinal DLBCL, Epstein-Barr virus-positive DLBCL, and primary cutaneous DLBCL. The study's primary endpoint, like that of the POLARIX study, is progression-free survival. Initial safety data on 127 patients demonstrated the tolerability of replacing vincristine with polatuzumab in the R-mini-CHOP regimen, with no difference in neuropathy events and hematologic toxicity in the two arms but a higher incidence of gastrointestinal side effects in patients treated with pola-R-mini-CHP.[24]

Glofitamab-pola-R-CHP

This is an ongoing phase Ib study (NCT03467373) adding the bispecific antibody glofitamab to the pola-R-CHP regimen. Initial results from 24 patients enrolled demonstrate a similar safety profile of glofitamab-pola-R-CHP and promising efficacy (overall response rate 100%, complete response rate 76.5%).[33] Another study (NCT04914741), a phase IB multicenter parallel arm open-label study of glofitamab-R-CHOP and glofitamab-pola-R-CHP, is ongoing in Australia.[34] An international randomized study has been initiated to compare the glofitamab-pola-R-CHP regimen with pola-R-CHP (NCT06047080 phase III, SKYGLO study) in previously untreated DLBCL patients with an IPI score greater than 1.

Rituximab-Polatuzumab-Glofitamab (R-Pola-Glo)

R-Pola-Glo is a German/Austrian phase II trial (EudraCT 2022-003398) targeting the older population of patients with previously untreated DLBCL. The study concluded the safety run-in phase in 2023 and early results highlighted the safety of this combination.[35]

Zanubrutinib-Polatuzumab-Rituximab (ZPR)

The combination of polatuzumab with zanubrutinib and rituximab is being investigated in another ongoing trial targeting untreated DLBCL in older patients (RCT 05940064). A recent update, including the first 12 patients treated with this regimen, demonstrated an overall response rate of 100% and rapid remission onset with a good safety profile.[36]

Polatuzumab vedotin for relapsed/refractory diffuse large B-cell lymphoma

Pola-BR

In the setting of DLBCL that relapses or is refractory to previous therapy, a phase II study of pola-BR compared the new regimen with standard BR for transplant-ineligible patients.[22] The study included a cohort of 80 patients with relapsed/refractory DLBCL after at least two lines of previous therapy who were randomly assigned 1:1 to either pola-BR or BR. Of note, the cohort did not include any cases of high-grade B-cell lymphoma.

The complete response rate, the primary endpoint of the study, was 40% (overall response rate, 63%) in the pola-BR group compared with 18% (overall response rate, 25%) in the BR alone group (P=0.026). After a median follow-up of 22.3 months, progression-free survival was superior with pola-BR than with BR alone (9.5 *vs*. 3.7 months, HR=0.36; HR=0.36, 95% CI: 0.21-0.63; P<0.001), as was overall survival (12.4 *vs*. 4.7 months, HR=0.42, 95% CI: 0.24-0.75; P=0.002) and duration of response (12.6 *vs*. 7.7 months). The overall survival benefit was also evident for subgroups of patients with dismal prognoses, such as refractory patients and those having already received multiple lines of prior therapy. The statistical differences in outcome between the two groups were somewhat unexpected, and some minor differences in the clinical characteristics of the patients might have been slightly unbalanced, although not found to be statistically significantly different given the study size.

The most common adverse events with the pola-BR combination (occurring in at least 20% of the patients) are listed in Table 2. Disease progression was the main reason for treatment discontinuation, occurring in 53.8% of the BR arm and 15.4% of the pola-BR arm. Fatal adverse events occurred in nine pola-BR patients and 11 BR patients, and were usually due to infections (4 in the pola-BR group and 4 in the BR group). After the randomized study was concluded, an extension cohort of 105 additional patients received pola-BR,[37] confirming the survival benefits and the general safety profile. Of note, nine patients received CAR T-cell therapy after pola-BR. However, given the well-documented bendamustine-induced lymphopenia, using this regimen before leukapheresis for CAR T-cell manufacturing might impair T cells and is usually avoided.

Ongoing trials

Pola-R-GemOx (POLARGO)

POLARGO is an ongoing phase III study of polatuzumab vedotin plus R-GemOx (rituximab, gemcitabine, oxaliplatin) *versus* R-GemOx in relapsed or refractory DLBCL (NCT04182204).[38] This study is being conducted in a relatively unfit/older population (the median age in the safety run-in was 76 years) and excludes patients who are eligible for autologous or allogeneic stem cell transplant. It is also expected that more than half of the patients will have refractory disease. The safety run-in data demonstrated that, with a careful strategy of dose interruptions/dose reductions, only grade 1 and 2 cases of peripheral neuropathy occurred, with no episodes of grade 3 toxicity. The cytopenia with pola-R-GemOx was comparable to that occurring with similar chemotherapy regimens for DLBCL in the relapsed/

refractory setting. In the preliminary report, the objective response rate was 40% (95% CI: 16-68), with 27% of the patients achieving a complete response and 47% of the patients experiencing progressive disease.[38] Accrual has been completed, and results are expected soon.

Pola-R-ICE

With the same concept of improving salvage therapy, but in this case before high-dose chemotherapy and autologous stem cell rescue or CAR T-cell therapy, an academic phase II study of polatuzumab combined with rituximab, ifosfamide, carboplatin, and etoposide (pola-R-ICE) has completed enrollment (NCT04665765). In 41 patients, the overall response rate was 91%, with 55% achieving a complete response, and the toxicity profile was acceptable.[39] A randomized study of pola-R-ICE *versus* R-ICE has already begun recruiting among centers of the German lymphoma group (NCT04833114).

Pola-mosunetuzumab

For heavily pre-treated patients with DLBCL and follicular lymphoma, a combination of polatuzumab vedotin with the bispecific antibody anti-CD3xCD20 mosunetuzumab[40] has demonstrated promising results in a phase Ib/II trial.[41] This trial was intended for patients who underwent several lines of treatment and were unfit or unable to receive high-dose chemotherapy or CAR T-cell therapy. Of 120 patients, 19.2% had high-grade B-cell lymphoma histology, 77.5% were refractory to their last prior line of treatment, while 35% and 12.5% had previously received CAR-T cell therapy or autologous stem cell transplant, respectively. The overall response rate was the primary efficacy endpoint for the study and was 62.4% (95% CI: 53.0-71.2%), with a complete response achieved in 50.4% of the patients (95% CI: 41.0-59.8%). The 2-year progression-free survival was 31.6% (95% CI: 21.9-41.3%). In the post-CAR T-cell population, the overall and complete response rates were 60.0% and 47.8%, respectively, with a median progression-free survival of 9.6 months (95% CI: 4.9-not estimable).

The most frequent adverse events were fatigue (46.7%), neutropenia (35.0%), nausea and diarrhea (23.5%). Cytokine release syndrome, related to the use of mosunetuzumab, was observed in 16.7% of the patients. Seven patients (5.8%) and 11 patients (9.2%) discontinued mosunetuzumab or polatuzumab, respectively. An international randomized clinical trial aimed at enrolling 222 participants with relapsed/refractory aggressive B-cell non-Hodgkin lymphoma (SUNMO, NCT05171647) to compare pola-mosunetuzumab to R-GemOx is currently recruiting.

Pola-glofitamab

The combination of polatuzumab and glofitamab, another approved anti-CD3xCD20 bispecific antibody, has demonstrated favorable results in patients with relapsed/refractory DLBCL.[42,43] The overall response rate in 109 patients was 78%, and the complete response rate was 56%. Among the 27 patients who had received prior CAR T-cell therapy, the overall response rate was 78% and the complete response rate was 44%. The median progression-free survival was 10.4 months (95% CI: 5.8-19 months). The most common adverse events were cytokine release syndrome (45%) and peripheral neuropathy (24.3%). Immune effector cell-associated neurotoxicity syndrome was reported in three patients and in all cases was grade 1-2.[42]

Perspectives

Studies of polatuzumab vedotin indicate that this antibody-drug conjugate represents a valuable therapeutic agent for patients with large B-cell lymphoma, improving the results achieved with previous standard regimens. Furthermore, the main toxicities, hematologic and neurological, related to microtubule inhibition by monomethyl auristatin E, are manageable in routine practice. Nevertheless, several questions remain open.

While POLARIX represents the first study to document a significant improvement in progression-free survival for newly diagnosed patients with DLBCL with an IPI score of 2 to 5, without the addition of toxicity besides the modestly increased risk of febrile neutropenia, whether pola-R-CHP represents the new standard of care for all these patients has been debated. Some have proposed privileging the use of this regimen in selected subgroups of patients with more unfavorable clinical or biological characteristics while sparing those patients with a high chance of cure with R-CHOP. However, subgroup analyses are considered to help to generate new hypotheses rather than to provide definite answers. These hypotheses would need to be further evaluated whenever feasible, considering the diversity and intricacies of the clinical and molecular characteristics of patients. The results of other randomized studies currently being performed in this setting, some of which use R-CHOP, will further enrich these considerations.

In patients who are not optimal candidates for classical cytotoxic agents, combinations of polatuzumab, such as those with bispecific antibodies, might also open new approaches to investigate in the first-line setting (NCT05798156).

In the relapse setting, combinations of polatuzumab vedotin with cytotoxic agents or bispecific antibodies are clearly effective. Several investigators also commonly use this drug without bendamustine for patients who are candidates for cellular therapy. However, the role of polatuzumab vedotin will undoubtedly evolve rapidly. Given the cumulative neurotoxicity of the toxin, patients who receive this drug as part of their front-line management should not be exposed to repeated doses of this agent. The development of cellular therapies with less toxicity (used in older patients and delivered as an outpatient) and the emergence of other active agents, such

as bispecific antibodies, will continue to reshape the field. Finally, the use of polatuzumab in other mature B-cell malignancies has been somewhat disappointing (in follicular lymphoma[44]) or remains emergent (in mantle cell lymphoma[45]). The mechanisms of resistance to this agent remain to be elucidated, but they might provide some insights regarding the variability of efficacy observed in some biological subtypes of lymphoma.

To answer these questions, clinical studies with appropriate correlatives are mandated and will hopefully allow further improvements in the outcome of lymphoma patients.

Disclosures

PG has received financial compensation for advisory board participation or consulting roles from AstraZeneca, Kyowa Hakko Kirin, and Secura Bio and research funding from Kite Pharma. GS has received financial compensation for advisory board participation or consulting roles from AbbVie, Atbtherapeutics, Beigene, BMS, Genentech/Roche, Genmab, Innate Pharma, Incyte, Ipsen, Janssen, Kite/Gilead, Merck, Modex, Molecular Partners, Nurix, Orna Therapeutics, and Treeline; is a shareholder of Owkin; and has received research support from AbbVie, Genentech, Genmab Janssen, Ipsen, and Nurix, which was managed by his institution.

Contributions

PG and GS wrote the manuscript, completed the bibliographic search, redacted the manuscript and approved the final version.

Funding

The present research was funded in part through the National Institutes of Health, National Cancer Institute Cancer Center Support (grant P30CA008748).

References

1. Coiffier B, Lepage E, Briere J, 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):235-242.
2. Pfreundschuh M, Kuhnt E, Trümper L, et al. CHOP-like chemotherapy with or without rituximab in young patients with good-prognosis diffuse large-B-cell lymphoma: 6-year results of an open-label randomised study of the MabThera International Trial (MInT) Group. Lancet Oncol. 2011;12(11):1013-1022.
3. Sehn LH, Salles G. Diffuse large B-cell lymphoma. N Engl J Med. 2021;384(9):842-858.
4. Coiffier B, Sarkozy C. Diffuse large B-cell lymphoma: R-CHOP failure-what to do? Hematology Am Soc Hematol Educ Program. 2016;2016(1):366-378.
5. Bartlett NL, Wilson WH, Jung SH, et al. Dose-adjusted EPOCH-R compared with R-CHOP as frontline therapy for diffuse large B-cell lymphoma: clinical outcomes of the phase III Intergroup Trial Alliance/CALGB 50303. J Clin Oncol. 2019;37(21):1790-1799.
6. Cunningham D, Hawkes EA, Jack A, et al. Rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone in patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: a phase 3 comparison of dose intensification with 14-day versus 21-day cycles. Lancet. 2013;381(9880):1817-1826.
7. Récher C, Coiffier B, Haioun C, et al. Intensified chemotherapy with ACVBP plus rituximab versus standard CHOP plus rituximab for the treatment of diffuse large B-cell lymphoma (LNH03-2B): an open-label randomised phase 3 trial. Lancet. 2011;378(9806):1858-1867.
8. Sehn LH, Martelli M, Trněný M, et al. A randomized, open-label, phase III study of obinutuzumab or rituximab plus CHOP in patients with previously untreated diffuse large B-cell lymphoma: final analysis of GOYA. J Hematol Oncol. 2020;13(1):71.
9. Nowakowski GS, Chiappella A, Gascoyne RD, et al. ROBUST: a phase III study of lenalidomide plus R-CHOP versus placebo plus R-CHOP in previously untreated patients with ABC-type diffuse large B-cell lymphoma. J Clin Oncol. 2021;39(12):1317-1328.
10. Younes A, Sehn LH, Johnson P, et al. Randomized phase III trial of ibrutinib and rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in non-germinal center B-cell diffuse large B-cell lymphoma. J Clin Oncol. 2019;37(15):1285-1295.
11. Davies A, Cummin TE, Barrans S, et al. Gene-expression profiling of bortezomib added to standard chemoimmunotherapy for diffuse large B-cell lymphoma (REMoDL-B): an open-label, randomised, phase 3 trial. Lancet Oncol. 2019;20(5):649-662.
12. Martin P, Bartlett NL, Chavez JC, et al. Phase 1 study of oral azacitidine (CC-486) plus R-CHOP in previously untreated intermediate- to high-risk DLBCL. Blood. 2022;139(8):1147-1159.
13. Habermann TM, Weller EA, Morrison VA, 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):3121-3127.
14. Jaeger U, Trneny M, Melzer H, et al. Rituximab maintenance for patients with aggressive B-cell lymphoma in first remission: results of the randomized NHL13 trial. Haematologica. 2015;100(7):955-963.
15. Thieblemont C, Tilly H, Gomes da Silva M, et al. Lenalidomide maintenance compared with placebo in responding elderly patients with diffuse large B-cell lymphoma treated with first-line rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone. J Clin Oncol. 2017;35(22):2473-2481.
16. Crump M, Leppä S, Fayad L, et al. Randomized, double-blind, phase III trial of enzastaurin versus placebo in patients achieving remission after first-line therapy for high-risk diffuse large B-cell lymphoma. J Clin Oncol. 2016;34(21):2484-2492.
17. Dornan D, Bennett F, Chen Y, et al. Therapeutic potential of an anti-CD79b antibody-drug conjugate, anti-CD79b-vc-MMAE, for the treatment of non-Hodgkin lymphoma. Blood. 2009;114(13):2721-2729.
18. Polson AG, Yu SF, Elkins K, et al. Antibody-drug conjugates targeted to CD79 for the treatment of non-Hodgkin lymphoma. Blood. 2007;110(2):616-623.
19. Pfeifer M, Zheng B, Erdmann T, et al. Anti-CD22 and anti-CD79B antibody drug conjugates are active in different molecular diffuse large B-cell lymphoma subtypes. Leukemia. 2015;29(7):1578-1586.
20. Palanca-Wessels MC, Czuczman M, Salles G, et al. Safety and

activity of the anti-CD79B antibody-drug conjugate polatuzumab vedotin in relapsed or refractory B-cell non-Hodgkin lymphoma and chronic lymphocytic leukaemia: a phase 1 study. Lancet Oncol. 2015;16(6):704-715.
21. Morschhauser F, Flinn IW, Advani R, et al. Polatuzumab vedotin or pinatuzumab vedotin plus rituximab in patients with relapsed or refractory non-Hodgkin lymphoma: final results from a phase 2 randomised study (ROMULUS). Lancet Haematol. 2019;6(5):e254-e265.
22. Sehn LH, Herrera AF, Flowers CR, et al. Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol. 2020;38(2):155-165.
23. Tilly H, Morschhauser F, Sehn LH, et al. Polatuzumab vedotin in previously untreated diffuse large B-cell lymphoma. N Engl J Med. 2022;386(4):351-363.
24. Jerkeman M, Leppä S, Hamfjord J, Brown P, Ekberg S, Ferreri AJM. Initial safety data from the phase 3 POLAR BEAR trial in elderly or frail patients with diffuse large cell lymphoma, comparing R-Pola-mini-CHP and R-mini-CHOP. Hemasphere. 2023;7(Suppl):e91359ec.
25. Tilly H, Morschhauser F, Bartlett NL, et al. Polatuzumab vedotin in combination with immunochemotherapy in patients with previously untreated diffuse large B-cell lymphoma: an open-label, non-randomised, phase 1b-2 study. Lancet Oncol. 2019;20(7):998-1010.
26. Horn H, Ziepert M, Becher C, et al. MYC status in concert with BCL2 and BCL6 expression predicts outcome in diffuse large B-cell lymphoma. Blood. 2013;121(12):2253-2263.
27. Cheson BD, Fisher RI, Barrington SF, 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):3059-3068.
28. Herrera AF, McCord R, Kimes P, et al. Risk profiling of patients with previously untreated diffuse large B-cell lymphoma (DLBCL) by measuring circulating tumor DNA (ctDNA): results from the POLARIX study. Blood. 2022;140(Supplement 1):1297-1300.
29. Wright GW, Huang DW, Phelan JD, et al. A probabilistic classification tool for genetic subtypes of diffuse large B cell lymphoma with therapeutic implications. Cancer Cell. 2020;37(4):551-568.e14.
30. Ennishi D, Jiang A, Boyle M, et al. Double-hit gene expression signature defines a distinct subgroup of germinal center B-cell-like diffuse large B-cell lymphoma. J Clin Oncol. 2019;37(3):190-201.
31. Morschhauser F, Leung W, Raghavan V, et al. Deciphering the clinical benefit of Pola-R-CHP versus R-CHOP in different genetic subtypes beyond cell of origin in the POLARIX study. Blood. 2023;142(Supplement 1):3000.
32. Lynch RC, Poh C, Ujjani CS, et al. Polatuzumab vedotin with infusional chemotherapy for untreated aggressive B-cell non-Hodgkin lymphomas. Blood Adv. 2023;7(11):2449-2458.
33. Dickinson M, Viardot A, Marks R, et al. Glofitamab + Pola-R-CHP in patients with previously untreated diffuse large B-cell lymphoma (DLBCL): results from a phase Ib study. J Clin Oncol 2023;41(16_suppl):7549.
34. Topp MS, Tani M, Dickinson M, et al. Glofitamab plus R-CHOP induces high response rates with a manageable safety profile in patients with previously untreated diffuse large B-cell lymphoma (DLBCL): a 12-month analysis from a phase Ib study. Blood. 2023;142(Supplement 1):3085.
35. Melchardt T, Wurm-Kuczera RI, Altmann B, et al. Feasibility and safety of the first-in-human chemotherapy-light combination of rituximab, polatuzumab vedotin and glofitamab in previously untreated aggressive B-cell lymphoma patients above 60 years of age ineligible for a fully dosed R-CHOP - R-Pola-Glo/Ikf-t062, a study of the Austrian Group for Medical Tumor Therapy (AGMT-NHL-16) and the German Lymphoma Alliance (GLA2022-10). Blood. 2023;142(Supplement 1):1734.
36. Ren Y, Zhuang J, Yuan L, Ji L, Ke Y, Liu P. Polatuzumab vedotin, zanubrutinib and rituximab achieved rapid and deep response in previously untreated frail and elderly diffuse large B-cell lymphoma patients. Blood. 2023;142(Supplement 1):1747.
37. Sehn LH, Hertzberg M, Opat S, et al. Polatuzumab vedotin plus bendamustine and rituximab in relapsed/refractory DLBCL: survival update and new extension cohort data. Blood Adv. 2022;6(2):533-543.
38. McMillan A. Initial safety run-in results of the phase III POLARGO trial: polatuzumab vedotin plus rituximab, gemcitabine and oxaliplatin in patients with relapsed/refractory diffuse large B cell lymphoma. J Clin Oncol. 2022;40(16_suppl):7551.
39. Herrera AF, Chen L, Crombie JL, et al. Polatuzumab vedotin combined with R-ICE (PolaR-ICE) as second-line therapy in relapsed/refractory diffuse large B-cell lymphoma. Blood. 2022;140(Supplement 1):1065-1067.
40. Budde LE, Ghosh N, Chavez JC, et al. Promising tolerability and efficacy results from dose-escalation in an ongoing phase Ib/II study of mosunetuzumab (M) with polatuzumab vedotin (Pola) in patients (pts) with relapsed/refractory (R/R) B-cell non-Hodgkin's lymphoma (B-NHL). J Clin Oncol. 2021;39(15_suppl):7520.
41. Budde LE, Olszewski AJ, Assouline S, et al. Mosunetuzumab with polatuzumab vedotin in relapsed or refractory aggressive large B cell lymphoma: a phase 1b/2 trial. Nat Med. 2024;30(1):229-239.
42. Hutchings M, Avigdor A, Sureda Balari AM, et al. Glofitamab plus polatuzumab vedotin continues to demonstrate frequent and durable responses and has a manageable safety profile in patients with ≥2L relapsed/refractory DLBCL, including HGBCL, and in patients with prior CAR T-cell therapy: updated results from a phase Ib/II study. Blood. 2023;142(Supplement 1):4460.
43. Hutchings M, Sureda A, Terol MJ, et al. Glofitamab (Glofit) in combination with polatuzumab vedotin (Pola): phase Ib/II preliminary data support manageable safety and encouraging efficacy in relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL). Blood. 2021;138(Supplement 1):525.
44. Flowers CR, Matasar MJ, Herrera AF, et al. Polatuzumab vedotin plus bendamustine and rituximab or obinutuzumab in relapsed/refractory follicular lymphoma: a phase Ib/II study. Haematologica. 2024;109(4):1194-1205.
45. Wang ML, Assouline S, Kamdar M, et al. Fixed duration mosunetuzumab plus polatuzumab vedotin has promising efficacy and a manageable safety profile in patients with BTKi relapsed/refractory mantle cell lymphoma: initial results from a phase Ib/II study. Blood. 2023;142(Suppl 1):734.