short review

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Diffuse large B-cell lymphoma

David Fuchs

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Summary Since the introduction of anti-CD20 antibodies and polychemotherapy, diffuse large B-cell lymphoma (DLBCL) has become a treatable, and, for a high proportion of patients, curable disease. However, a sizeable proportion of patients, especially in poor-prognosis subgroups, will relapse.
The landscape of therapy in DLBCL has seen some exciting changes in the past years, most notably with the introduction of CAR-T-cell therapy. All three major trials were recently updated and showed sustained responses and excellent preliminary survival data.
Other immunotherapies are gaining ground as well, as the antibody–drug conjugate polatuzumab vedotin has shown to be effective in relapsed DLBCL in combination with chemo-immunotherapy (rituximab and bendamustine). Complete remission rates increased from 15 to 40% and overall survival from 4.7 to 11.8 months. Polatuzumab is also being studied in previously untreated patients and results are awaited in 2019.
Checkpoint inhibitors, the mainstay of therapy in a variety of malignancies, are also being studied in DLBCL. Interim results of an ongoing phase I/II study of atezolizumab with R-CHOP in previously untreated patients show 83% complete remissions in early data. Other novel substances, like anti-CD47-antibodies and PI3-kinase inhibitors, show promising efficacy in early trials in relapsed patients as well.

D. Fuchs (✉)
Kepler Universitätsklinikum, Klinik für Interne 3 – Hämatologie und medizinische Onkologie, Med Campus III, Johannes Kepler Universität Linz, Krankenhausstraße 9, 4020 Linz, Austria
david.fuchs@kepleruniklinikum.at

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Introduction

Since the introduction of anti-CD20 antibodies and polychemotherapy, diffuse large B-cell lymphoma (DLBCL) has become a treatable, and, for a high proportion of patients, curable disease. However, a sizeable proportion of patients will experience relapse [1]. Patients with dual translocations in the myc, bcl2, and/or bcl6 oncogenes, recently recognized as a distinct entity in the WHO classification (high-grade B-cell lymphoma, with myc and bcl2 and/or bcl6; double- or triple-hit lymphoma), have a particularly grave prognosis, with less than 33% of patients achieving long-term survival [2, 3].

A variety of strategies have been employed to provide better outcomes, especially in these high-risk patients, with little success. Intensification of therapy with dose-adjusted R-EPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) in high-risk patients (i. e., double hit or double expressor) with DLBCL has shown superior progression-free survival (PFS; 22.16 vs. 12.14 months, $p = 0.032$) and a trend for longer overall survival (OS; 31.37 vs. 21.43 months, $p = 0.186$) compared with the standard R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) in a meta-analysis of retrospective studies and has become the standard approach for these patients [2].

Adding new drugs to R-CHOP has failed so far, most notably with ibrutinib, bortezomib, lenalidomide, and bevacizumab [4]. Numerous trials are pursuing other combinations, some of which will be discussed here.

In relapsed or refractory DLBCL, especially when second-line therapy with autologous stem cell trans-

plantation has failed, prognosis is grim, with a median survival of only 6.2 months and a 2-year OS rate of 19% [5].

In this setting, novel therapies, most notably CAR-T-cell therapy, have made exciting progress.

This review will present, in a concise manner, the most important developments in DLBCL in recent months.

Antibody–drug conjugates

Antibody–drug conjugates such as trastuzumab emtansine and brentuximab vedotin have been a mainstay in advanced breast cancer and for Hodgkin's disease [6, 7]. These compounds allow the targeted delivery of chemotherapeutic agents to target cells without excessive toxicity.

CD79b is a part of the B-cell receptor complex and is expressed on mature B-cells and on B-cell malignancies, including DLBCL [8].

Polatuzumab vedotin (Pola), an antibody–drug conjugate with the antimitotic agent monomethyl auristatin E (MMAE), targets CD79b. It has previously demonstrated efficacy as monotherapy in relapsed or refractory (r/r) DLBCL with an overall response rate (ORR) of 56% [9]. In the phase II ROMULUS trial, ORR on Pola with an anti-CD20 antibody was 56% (17% complete remission, CR; [10]).

Data on a randomized phase II trial in r/r DLBCL with rituximab (R) and bendamustine with or without Pola were recently reported [11]. In total, 80 patients with follicular lymphoma (FL) and 80 patients with DLBCL were randomized 1:1 to receive R-bendamustine (rituximab 375 mg/m^2 on day 1 and bendamustine 90 mg/m^2 on days 1 and 2 for six cycles; every 28 days for FL and every 21 days for DLBCL) with or without Pola (1.8 mg/kg).

Patients had had a median of two prior lines of therapy (range 1–5 for the control group and 1–7 for the experimental group), 15 (control) and 23% prior autologous stem cell transplantation, and almost all patients (98% in both groups) had received prior anti-CD20 therapy.

In DLBCL patients, the addition of Pola increased CR rates (40 vs. 15%) and both median PFS (6.7 vs. 2 months) and OS (11.8 vs. 4.7 months). These benefits could be shown in all lines of therapy.

Toxicity was increased with the addition of Pola, particularly hematological toxicity (febrile neutropenia, 12 vs. 5%; anemia, 18 vs. 6%; neutropenia 40 vs. 26%). A special area of concern is peripheral neuropathy, which was seen in 38% of patients in the experimental arm (grade 1, 25%; grade 2, 13%; grade 3–4, 1%).

Based on this study, Pola received breakthrough therapy and PRIME status by the United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) for r/r DLBCL.

In the first-line setting, because of the vincristine-like mode of action of MMAE, Pola is being evaluated as a replacement for vincristine in R-CHOP (rituximab, doxorubicin, cyclophosphamide, vincristine, prednisone) regimens. After initial positive results in a phase Ib/II study (45 patients, Pola with R-CHP, 91% ORR, 78% CR), a randomized, double-blind, placebo-controlled phase III study (POLARIX), which randomizes patients with newly diagnosed DLBCL to either R-CHOP or Pola with R-CHP, is underway and is scheduled to be completed in 2019 [12, 13].

Checkpoint inhibitors

Checkpoint inhibitors, which are well established in solid malignancies and Hodgkin's lymphoma, are also being evaluated in DLBCL [14].

Early results in r/r DLBCL have shown a 36% ORR with nivolumab, an anti-PD-1 antibody, 16% ORR with atezolizumab, a fully humanized anti-programmed death-ligand 1 (PD-L1) antibody in combination with the CD20-antibody obinutuzumab, and a 20% ORR with a combination of nivolumab and the anti-CTLA4-agent ipilimumab [15–17].

Combinations of checkpoint inhibitors with other therapies, especially chemotherapy, are being studied extensively. Interim results of an ongoing phase I/II study of atezolizumab with R-CHOP in first-line therapy were recently reported [18]. In total, 42 patients with advanced DLBCL (stage III/IV and IPI >1; or stage II with bulky disease ≥7 cm) were included and were treated with six to eight cycles of R-CHOP-21 combined with atezolizumab (1200 mg on day 1, starting from cycle 2). Patients in CR were then consolidated with atezolizumab at the same dose and schedule for 12 months. An interim analysis of 15 patients showed an 83% CR rate (modified Lugano criteria; 73% with Cheson criteria); 13% had progressive disease.

Only three patients had immune-related adverse events (increases in transaminases and lipase), while chemotherapy-related toxicity from R-CHOP was not increased (neutropenia, 38%; febrile neutropenia, 9.5%; no therapy-related deaths).

The combination of chemo-immunotherapy and checkpoint inhibition appears safe and shows encouraging response rates, with a CR rate of 83% compared with historical data reporting a CR rate of 75% [1].

CAR-T cells

Chimeric-antigen-receptor (CAR) T-cell therapy uses genetically modified T-cells that express an antigen-specific receptor, which allows for a specific immune reaction against the antigen-carrying cell. A CAR consists of an antigen recognition domain, a transmembrane domain, one or more intracellular co-stimulatory domains, and a signaling domain.

Three major products with CD19 as the therapeutic target are currently in clinical trials (axi-cel; ZUMA-1 trial; tisagenlecleucel, JULIET trials and liso-cel, TRANSCEND trial). The three compounds differ in their co-stimulatory domains (axi-cel uses CD28, while liso-cel and tisagenlecleucel use CD137) and in their CD4:CD8 ratio (1:1 fixed ratio in liso-cel; [19]).

All three major studies involving these compounds were updated at the 2018 ASCO and EHA conferences.

ZUMA-1 was a phase I/II study with anti-CD-19 CAR-T-Cells in r/r DLBCL. The ORR was 82%, which led to a recent FDA approval [20]. Durability of response and outcomes by prior lines of therapy were presented.

With a median follow-up of 15.1 months, ORR remained unchanged from a previous analysis (8.7 months of follow-up), and CR rates increased from 54 to 58%. Patients who achieved stable disease or better (disease control) had a 73% PFS at 12 months. For patients who achieved CR or PR, the 12-month PFS was 79 and 78%, respectively [20].

In total, 57% of patients had two or three prior lines of therapy and 40% had had four or more. Patients with two to three prior lines of therapy had better ORR (94% vs. 67%) and CR rates (65% vs. 53%) and a better 12-month OS (65% vs. 51%) than patients with four or more prior therapies. Adverse events of grade 3 and higher did not differ between the groups [21].

The JULIET trial was a phase II trial in the same setting as ZUMA-1 and was updated with longer-term follow-up [22].

In this trial, 111 patients were treated (of 165 enrolled). The data, now with 13.9 months of median follow-up, show an ORR of 52% with 40% CR. ORR rates did not differ between patients with prior autologous stem cell transplantation ($n=41$ patients) and those without (50% for patients without and 54% for patients with prior stem cell transplantation).

At 12 months, 65% of responding patients were still in remission, and thus median duration of response was not yet reached. Median OS was 11.7 months for all treated patients, and 49% were alive at 12 months. These data confirm earlier reports and show that durable remission can be achieved with CAR-T-cell therapy.

A long-term follow-up of 91 patients from the TRANSCEND trial was presented at the 2018 ASCO meeting as well [23]. In this trial, 91 patients were treated in a dose-finding and a pivotal (CORE) cohort. Updated survival data for the full and the CORE cohort were recently presented.

Patients in the CORE cohort had an ORR of 49% (46% CR). Similar response rates were seen in patients with double- or triple-hit lymphoma (ORR: 62.5%, $n=16$) and patients with a relapse of less than 12 months after autologous stem cell transplantation (ORR: 53.3%, $n=15$).

Patients in CR in the CORE cohort had an OS of 89% at 12 months, while patients in PR had a median OS of 10.3 months, with 33% still alive after 12 months.

Of patients who were in CR at 3 months, 88% still had a CR at 6 months, while the duration of response in patients in PR was only 2.1 months.

Anti-CD47

A novel immune-based approach is 5F9, an anti-CD47 antibody. CD47-targeting improved tumor cell phagocytosis and T-cell mediated cytotoxicity, which suggests synergism with rituximab by enhancing cellular phagocytosis [24].

5F9 was explored in combination with rituximab in a phase I trial with 22 patients, 15 of whom had relapsed or refractory DLBCL, with a median of four prior lines of therapy. Patients were treated with escalating dosses of 5F9 and standard dose of rituximab.

The ORR in DLBCL was 40% (27% CR). Toxicity was tolerable, with grade 3 chills, fever, and anemia.

Anti-CD19 MorphoSys antibody

CD19 is not only targeted by CAR-T-cell therapies, but also by MOR208, an Fc-engineered, humanized, monoclonal antibody in clinical development in combination approaches with lenalidomide or bendamustine in patients with relapsed and refractory DLBCL. MOR208 does have single agent activity (ORR 26% in r/r DLBCL), but is primarily studied in combination with lenalidomide or bendamustine [25]. While there are no results with the latter approach to date, data on the combination with lenalidomide (L-MIND) were recently shown at ASH [26].

Patients with r/r DLBCL who had between one and three prior lines of therapy were treated with lenalidomide (25 mg, days 1–21 of a 28-day cycle) and MOR208 (weekly in cycles 1–3 with a loading dose on day 4 of cycle one; bi-weekly from cycle 4). The ORR was 52% (CR: 32%, PR: 20%) and the median PFS was 11.3 months. Common side effects were neutropenia, thrombocytopenia, anemia, diarrhea, and rashes.

PI3K inhibition

A PI3Kδ inhibitor (ACP-319) was evaluated in combination with acalabrutinib (a Bruton tyrosine kinase inhibitor) in patients with relapsed and refractory B-cell lymphoma [27]. A cohort of 25 DLBCL patients was presented (nine with GCB and 16 non-GCB DLBCL). The median number of prior therapies was 2 and the median age was 70. No responses were seen in the GCB cohort, but non-GCB patients experienced an ORR of 63% (CR: 25%, PR: 38%). Median PFS was 5.5 months for non-GCB patients and 1.8 months for GCB patients.

Adverse events were diarrhea (52%), fatigue (40%), and rash (40%). There were no therapy-related deaths.

Another pan-class I PI3K-inhibitor, buparlisib, was evaluated in a phase I/II trial combined with ibrutinib in patients with r/r DLBCL, follicular lymphoma, and mantle cell lymphoma [28]. Of 37 patients in the trial, 14 hat DLBCL (five FL, 15 mantle cell lymphoma). The ORR rate in DLBCL was 31% (three patients with CR, one with PR). Toxicity (grade 3/4) included rash, hyperglycemia, diarrhea, and hypertension.

PI3K inhibition is an interesting pathway for therapy, although data are still immature. In the buparlisib trial, there was no information (at least as of yet) on GCB/non-GCB subtype, which may explain the differences in ORR seen between the two trials.

Conclusion

Immunotherapy has been the dominating theme in DLBCL therapy in the past months. In first-line therapy, addition of either polatuzumab vedotin or checkpoint inhibitors to R-CHOP has shown encouraging response rates. In relapsed DLBCL, polatuzumab vedotin has already shown improved survival when compared with R-bendamustine in a randomized trial; however, it remains to be seen whether these benefits are also applicable in a much better prognosis group of patients and with R-CHOP as a backbone.

Therapy of relapsed and refractory DLBCL is an area of high unmet need, and novel approaches, especially CAR-T-cell based therapies, have shown exciting data in early trials, which led to regulatory approval in the United States and Europe. Still, a sizeable proportion of patients will either not be able to receive these compounds or will relapse despite treatment, which still leaves need for other therapeutic options in this setting.

Although it remains to be seen which role new compounds will eventually play in the therapeutic landscape, and there are challenges in toxicities, cost, and large-scale manufacturing, change is happening, and for the better.

Take-Home Message

- Antibody–drug conjugates are effective in combination with chemo-immunotherapy and are being studied in previously untreated patients.
- CAR-T-cell therapy showed sustained and durable responses and excellent survival data.
- Checkpoint inhibition is an interesting concept in combination with chemotherapy.

Conflict of interest D. Fuchs declares that he has no competing interests.

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