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T-CELL AND OTHER LYMPHOPROLIFERATIVE MALIGNANCIES (J ZAIN, SECTION EDITOR)

Treatment of Aggressive B Cell Lymphomas: Updates in 2019

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Abstract

Purpose of Review Recent years have seen the development of gene expression profiling and next-generation sequencing in diffuse large B cell lymphoma (DLBCL), leading to a more defined characterization of this disease into distinct subentities. The genomic era has ushered in the possibility of using precision guided therapy, in part based on targeting genes with somatic mutations. Such precision-targeted therapies will ultimately reduce the need for chemotherapy, induce fewer adverse events, and likely enhance the cure rate for these patients. Here, we discuss emerging therapeutic strategies that have been recently developed for the upfront and relapse setting of DLBCL.

Recent Findings Clinical trials exploring precision medicine have showed promising results; however, attempts to enhance frontline immunochemotherapy by adding targeted agents to the R-CHOP backbone did not confirm the expected benefit. The last decade has also seen a revolutionary development of immunotherapy in B cell lymphomas. While cellular immunotherapy demonstrated a striking success of CAR T cells in DLBCL, checkpoint inhibitors have lacked success in B cell lymphomas. A parallel therapeutic expansion has involved bispecific monoclonal antibodies as a powerful tool for redirected T cell therapy independently from costimulatory molecules and major-histocompatibility complex.

Summary The landscape of drugs for the treatment of DLBCL has become overwhelmed by the increasing number of targeted and immunological therapies; however, none have enhanced efficacy of frontline therapy. Future direction should focus to redefine therapeutic paradigm and develop mechanism-based combinatorial regimens specifically tailored for DLBCL genetic subgroups.

Keywords Diffuse large B cell lymphoma · Ibrutinib · Lenalidomide · Venetoclax · CAR T cells · Immunotherapy

Introduction

Diffuse large B cell lymphoma (DLBCL) is the most common aggressive lymphoma, accounting for about 30% of all new diagnosis of non-Hodgkin lymphoma (NHL) [1]. Despite its uniform morphology, DLBCL is a very heterogenous disease at the molecular level. Gene expression profiling (GEP) studies have identified two main subgroups based on the cell of origin (COO): germinal center B cell (GCB) and activated B cell (ABC) [2]. These two subtypes have distinct oncogenic driver pathways resulting in different prognosis. In particular, GCB has about 70–80% cure rate with the current mainstay therapy R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) while ABC has about 40% [3]. In 2018, a novel approach using a multiplatform analysis of structural genomic abnormalities and gene expression has provided a new and evolving understanding of the pathogenesis of DLBCL and the molecular characteristics that may influence therapeutic response [4, 5]. Schmitz et al. analyzed 574 fresh frozen samples of newly diagnosed DLBCL [4••]. They identified four subtypes: the first one is more frequent among ABC and characterized by MyD88 and CD79B mutations (MCD); the second subtype is characterized by BCL6 fusion and NOTCH2 mutations (BN2) and is represented equally among ABC and GCB; the third is characterized by NOTCH1 mutations (N1) and is more frequent in ABC; the last one is characterized by EZH2 mutations and BCL2

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translocation (EZB) and is more frequent in GCB. Overall, these genetic subtypes covered 46.6% of cases. An analysis of clinical outcome was possible for 117 patients treated with R-CHOP whose tumor falls in one of the genetic subtypes. The 5-year overall survival (OS) was 26%, 36%, 65%, and 68% for MCD, N1, BN2, and EZB respectively [4••]. In a separate study, Chapuy et al. performed whole-exome sequencing of 304 untreated DLBCL to detect low-frequency mutations, somatic copy number alterations, and structural variants [5••]. They identified five distinct DLBCL subsets: cluster 5 has mutations in MyD88 and CD79 as well as gain in chromosome 18q with increased expression of BCL2 and MALT1 and is more frequent in ABC group; cluster 1 presents BCL6 single variants and NOTCH2 mutations and is also more often in ABC type; cluster 3 is characterized by BCL2 translocations and alteration of PTEN and a poor risk GCB group; cluster 4 is a favorable risk GCB group with alteration in BCR/PI3K, JAK/STAT, and BRAF pathway; and cluster 2 is a COO-independent group with frequent biallelic inactivation of TP53, loss of CDKN2A, and genomic instability [5••]. The genetic subtypes identified by the 2 groups are overlapping (cluster 5 corresponding to MCD, cluster 2 to BN2, and cluster 3 to EZB) and provide a superior molecular homogeneity than COO, which allows splitting GCB and ABC groups into biologically distinct subgroups. This will help in targeting specific vulnerabilities and personalizing treatment approach in DLBCL. Herein, we provide an overview of the most important updates on DLBCL treatment of the last years.

Early-Stage DLBCL

While young patients with DLBCL are typically treated with six cycles of R-CHOP, results from the FLYER trial suggest that a subgroup of young patients with favorable-prognosis disease can achieve the same clinical benefit with four cycles of R-CHOP plus two cycles of rituximab monotherapy [6•]. In this trial, patients with age between 18 and 60 years were randomized to receive either six cycles ($n = 295$) or four cycles of R-CHOP plus two cycles of rituximab ($n = 297$). Most patients had stage I-II disease and low-risk disease [age-adjusted international prognostic index (aaIPI) of 0 and non-bulky disease (< 7.5 cm)]. At a median follow-up of 66 months, the rates of 3-year progression free survival (PFS), event-free survival (EFS), and OS were similar between each group: PFS was 94% with 6 cycles vs. 96% with 4 cycles (hazard ratio [HR] = 0.9; 95% CI 0.5–1.6; $p = 0.8$), EFS 89% vs. 89% (HR = 1.0; 95% CI 0.7–1.6; $p = 0.9$), and OS 98% vs. 99% (HR = 0.8; 95% CI 0.4–1.9; $p = 0.67$). Reducing the number of CHOP cycles from six to four also reduced the number of adverse events by approximately one-third. Cytopenias were more frequent in the six-cycle group (80% and 60%), and overall, two therapy-related deaths were observed in the six-cycle arm and none in the four-cycle arm. However, longer-term follow-up is needed to monitor delayed toxicity. [6•]

Another recent trial demonstrated that early-stage DLBCL patients can safely skip radiation treatment after a clear PET scan [7]. Radiation can be painful, causes rashes or burns, and increases patients' risk of secondary cancers. In the S1001 SWOG trial, 132 patients with stage I–II DLBCL were enrolled, with no age limit. Hence, patients skewed older, with a median age of 62 years. All patients received R-CHOP therapy followed by a PET scan after their third cycle of treatment. Patients with PET negative received one additional cycle of R-CHOP to complete their treatment, for a total of four rounds of chemotherapy. Patients with PET positive underwent involved-field radiation therapy (IFRT) to their affected lymph nodes and a booster treatment in areas where the scans showed fast-growing cancer cells. Three to 6 weeks later, these patients received treatment with 90 Y-ibritumab tiuxetan. At a median follow-up of 5 years, 91% of people who received no radiation were alive and 89% were cancer-free compared to 93% of patients who did receive radiation, 86% of whom were cancer-free [7]. Together with the FLYER trial in younger patients, the S1001 SWOG trial established R-CHOP × 4 alone as the new standard approach to limited stage disease for DLBCL patients with negative PET scan [6, 7].

Advanced-Stage DLBCL

R-CHOP-X

Although R-CHOP is currently the mainstay therapy for DLBCL, this treatment fails to cure at least 40% of patients [8]. In particular, ABC DLBCL has a poor prognosis when treated with standard chemotherapy regimens [3, 9–12]. In this subset, a variety of genetic alterations that aberrantly activate the B cell receptor (BCR) and Toll-like receptor (TLR) signaling pathways has been linked to the constitutive activation of nuclear factor kappa B (NF-kB) [12]. In the BCR pathway, mutations in CD79 and CARD11 are the most frequently observed genetic alterations, whereas L265P mutation of the signaling adaptor MyD88 is the most frequent one that constitutively activate the TLR pathway [13]. Several efforts have been attempted to improve the standard frontline treatment R-CHOP by adding a novel targeted drug to the backbone regimen (R-CHOP-X). However, up to now, none of them has demonstrated superiority compared to R-CHOP.

Ibrutinib

In the BCR pathway, selective targeting of the Bruton tyrosine kinase (BTK), which links BCR to NF-kB, has been showed to induce cell death of ABC DLBCL [13, 14]. In a phase I/II

clinical trial that involved 80 patients with relapsed/refractory (R/R) DLBCL, the BTK inhibitor ibrutinib produced a 37% response rate in ABC DLBCL [15]. The response to ibrutinib was correlated with MyD88 mutation, which occurs in 40% of [30] ABC DLBCL. In particular, isolated MyD88 mutations were associated with resistance to ibrutinib, whereas lymphomas with concurrent MyD88 and CD79 mutations remained sensitive to ibrutinib. Nevertheless, these responses were mainly partial and of a short duration [15], raising the question whether a combined inhibition of MyD88 and ibrutinib would have resulted in a better treatment outcome. Recently, HDAC inhibitors have been demonstrated to inhibit MyD88 transcription [29] and enhance antiproliferative activity of ibrutinib against ABC DLBCL harboring MyD88 mutation [16], providing the mechanistic rational for an ongoing clinical trial evaluating the combination of abexinostat and ibrutinib in R/R DLBCL (MSKCC protocol 19-080). Recently, the phase III PHOENIX trial evaluated ibrutinib in combination with R-CHOP in untreated non-GCB DLBCL [17]. A total of 838 patients were randomly assigned to R-CHOP plus ibrutinib ($n = 419$) or placebo ($n = 419$). Median age was 62.0 years; 75.9% of evaluable patients had ABC-subtype disease. Ibrutinib plus R-CHOP did not improve EFS in the intent-to-treat (HR = 0.934) or ABC (HR = 0.949) population. In patients aged younger than 60 years, ibrutinib plus R-CHOP improved EFS (HR = 0.579), PFS (HR = 0.556), and OS (HR = 0.330) and slightly increased serious adverse events (35.7% vs 28.6%). In contrast, in patients aged 60 years or older, ibrutinib plus R-CHOP worsened survival, increased serious adverse events (63.4% vs 38.2%), and decreased the proportion of patients receiving at least six cycles of R-CHOP (73.7% vs 88.8%) [17]. Despite the advantage in young patients, this study did not meet its primary end point. One possible explanation might be the resistance to ibrutinib induced by MyD88 mutation [16]. Genomic analysis is ongoing and will try to shed some light on the results of this negative trial.

Lenalidomide

Lenalidomide, an oral immunomodulatory drug (IMiD) that has direct and indirect antineoplastic effect [14, 18], has showed high activity in the unfavorable ABC subtype [19–21]. Two phase II trials investigating the efficacy of lenalidomide plus R-CHOP (R^2-CHOP) in DLBCL found that lenalidomide overcomes the negative prognostic impact of the non-GCB phenotype [22, 23]. However, the phase III ROBUST trial which randomized newly diagnosed ABC-subtype DLBCL to receive R-CHOP plus either lenalidomide (15 mg/day oral lenalidomide, days 1–14) or placebo did not confirm superiority of this combination based on COO subgroup determined using centrally NanoString Analysis System. A total of 570 ABC DLBCL patients were enrolled in ROBUST ($n = 285$ per arm) with a median age of 65 years. Positive PFS trends favoring R^2-CHOP over placebo/R-CHOP were observed with disease stage III/IV (HR = 0.81; 95% CI 0.60–1.10) and IPI score ≥ 3 (HR = 0.74; 95% CI 0.53–1.05). Median EFS was not reached for either arm (HR = 1.04; 95% CI 0.80–1.34; $P = 0.73$). Overall response rate (ORR) was 91% for both arms, with 69% vs 65% complete response (CR) for R^2-CHOP vs placebo/R-CHOP, respectively. At a median follow-up of 27.1 months, 2-year OS was 79% for R^2-CHOP and 80% for placebo/R-CHOP. The most common grade 3/4 AEs for R^2-CHOP vs placebo/R-CHOP were myelosuppression [neutropenia (60% vs 48%), anemia (22% vs 14%), thrombocytopenia (17%vs 11%), leukopenia (14% vs 15%)] and febrile neutropenia (14% vs 9%) [24]. Despite a positive trend favoring R^2-CHOP in advanced stage and higher-risk patients, the ROBUST trial did not meet the primary endpoint of PFS.

At the same time of the ROBUST trial, the phase II ECOG 1412 study randomized 280 DLBCL patients to R^2-CHOP vs placebo/R-CHOP. However, the patients were not differentiated based on COO subtypes and the schedule of lenalidomide was different than ROBUST trial with higher dose for a shorter time (25 mg/daily for 10 days). This design wanted to maximize the synergy between R-CHOP and lenalidomide and yet allow hematological recovery before the following cycle. Unlike the ROBUST trial, the time from enrollment to treatment was very short since centralized pathology review was not necessary. The ECOG 1412 showed improvement in PFS in patients treated with R^2-CHOP with statistically significant 34% reduction in risk of death or progression. There was also a positive trend in OS and ORR towards improved outcome. COO was performed in 234 patients. In the 40% ABC subtype, there was a trend towards improved PFS and OS for patients treated with R^2-CHOP as opposed to R-CHOP alone. However, the ECOG 1412 is a phase II trial in contrast to ROBUST which is a phase III. The negative results of these studies unveil the need to move towards doubles or triplets to add to the CHOP backbone. Following this new concept, the phase II Smart Start trial evaluated lead-in treatment with rituximab, lenalidomide (25 mg on day 1–10), and ibrutinib (560 mg daily) in patients with newly diagnosed DLBCL [25]. The lead-in regimen was administrated for 2 cycles, and then combined with standard chemotherapy consisting of CHOP or EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin) for additional 6 cycles [25]. This trial builds on prior data presented at the 2018 ASH meeting, which showed that the combination of ibrutinib, lenalidomide, and rituximab was associated with a response rate of over 50% among R/R non-GCB DLBCL [26]. The Smart Start trial enrolled 60 patients, many of who were old and with comorbidities. After the first 2 cycles of rituximab, lenalidomide, and ibrutinib alone, the ORR was 86%, with a CR rate of 36%. After 2 cycles of this lead-in regimen alone followed by 2 cycles of this regimen plus

chemotherapy, the ORR was 100%, including a CR rate of 73%. At the end of all 8 treatment cycles, the ORR in 49 patients was 100%, with a CR rate of 96%. Most patients showed a dramatic reduction in disease burden after the first 2 cycles of rituximab, lenalidomide, and ibrutinib, with continuing reductions in disease burden during subsequent treatment cycles. The median OS was not reached (range, 74–938 days) and 1-year OS was 96%. The most common AEs of any grade consisted of nausea, peripheral sensory neuropathy, and diarrhea. The most common grade 3/4 AE was myelosuppression. One patient died from febrile neutropenia. Another patient developed a fatal central nervous system aspergillosis, which was attributed to the combination of a high-dose corticosteroid plus rituximab, lenalidomide, and ibrutinib. As a result, the use of corticosteroids was subsequently prohibited during the first 2 cycles of rituximab, lenalidomide, and ibrutinib. No further fungal infections were observed [25]. This study provides early data suggesting that rituximab, lenalidomide, and ibrutinib might be an important up-front regimen for patients who are not candidates for chemotherapy or who cannot tolerate standard induction therapies. Additional studies will likely evaluate whether the use of this regimen up-front will allow these patients to receive less chemotherapy afterward.

BCL2-Inhibitor

Given the frequent alteration in BCL2 in DLBCL, there has been great interest in developing BCL2 inhibitors (BCL2i) such as venetoclax in this disease. Despite highly active in chronic lymphocytic leukemia, modest results were observed in DLBCL [27]. In the phase I study evaluating venetoclax in 109 NHL patients, 34 of whom were DLBCL, there was only an ORR of 18% with a CR rate of 12% in the DLBCL subset [28]. The sensitivity to BCL2i in DLBCL has been associated with PMAIP1/NOXA gene amplification, which is a rare event [29]. In addition, blocking BCL2 alone is not enough to kill most lymphoma cells because the feedback on the antiapoptotic protein MCL1. Besides direct drug targeting of MCL1, HDAC inhibitors have been proposed as means to downregulate MCL1 expression and enhance BCL2i activity [29]. Based on these preclinical data, currently, a phase I trial is evaluating the efficacy and safety of CUDC-907, a dual-inhibitor of HDACs and PI3K [30], combined with BCL2i in R/R DLBCL (MSKCC protocol 13–045). BCL2i has showed promise also when combined with other three agents targeting unique survival pathways in the phase Ib study called ViPOR (venetoclax, ibrutinib, prednisone, obinutuzumab, and lenalidomide). Twenty-seven R/R B cell lymphomas (13 of whom DLBC) were enrolled. Of 21 patients off-therapy, 20 were evaluable for response with an ORR of 70% and 40% CR, and with ORR and CR rate of 69% and 25% in aggressive lymphomas. Median time to relapse and duration of response (DOR) was 1.35 months and not reached, respectively [31]. Recently, the results of the phase II CAVALLI study investigating the efficacy of venetoclax plus R-CHOP in 208 newly diagnosed DLBCL patients were reported [32]. There was an advantage for patients with BCL2 overexpression or translocation in a non-randomized comparison with the Goya phase III trial. The addition of venetoclax to R-CHOP resulted in improved efficacy in BCL2+ (70% vs 47.5%) and double hit lymphoma (DHL, 71.4% vs 25.0%) patients compared to the matched controls. Higher rates of cytopenia, infection, and febrile neutropenia were observed in the CAVALLI versus R-CHOP arm [32]. These data support further exploration of venetoclax + R-CHOP in a high-risk population of BCL2+ and DHL patients.

Bortezomib

Bortezomib (Velcade) is a proteasome inhibitor able to suppress NF-kB activity. Since the aberrant activation of this pathway is prevalent in ABC DLBCL, bortezomib has showed higher efficacy in this lymphoma subsubtype [33]. The phase II study LYM-2034 investigated bortezomib as a replacement for vincristine within the R-CHOP regimen (VR-CAP) in previously untreated non-GCB DLBCL patients. No significant difference in response rates and long-term outcomes were observed compared to R-CHOP [34]. Similarly, the phase II PYRAMID trial evaluated the efficacy and safety of R-CHOP vs VR-CHOP in previously untreated non-GCB DLBCL patients. Also, in this study, there was no difference between the two regimens [35]. However, both trials stratified patients based on IHC and not GEP. The phase III REMoDL-B trial randomized 1128 newly diagnosed ABC-subtype DLBLC defined by central GEP assay to receive VR-CHOP vs R-CHOP. At a median follow-up of 19.7 months, there was no difference in PFS (30-month PFS 70.1%, 95% CI 65.0–74.7 vs 74.3%, 95% CI 0.65–1.13; $p = 0.28$). The most common grade 3 or worse AE was hematological toxicity, reported in 178 (39.8%) of 447 patients given R-CHOP and 187 (42.1%) of 444 given VR-CHOP. Serious AEs occurred in 190 (42.5%) patients given R-CHOP, including five treatment-related deaths, and 223 (50.2%) given VR-CHOP, including four treatment-related deaths [36]. Further investigation of such an approach might be of interest in the poor prognosis population of DHL.

EZH2 Inhibitors

One of the emerging targets in DLBCL is the epigenetic modifier protein EZH2, a core component of the polycomb repressive complex 2 (PRC2) that methylases histone H3 lysine 27 (H3K27) to form H3K27me3, a histone mark associated with gene repression. Approximately 30% of GCB-type DLBCL tumors and follicular lymphomas (FLs) have an activating mutation in EZH2 [37], resulting in aberrant trimethylation

of H3K27 and consequent transcriptional silencing. Normally, EZH2 levels decrease as B cells exit the germinal center (GC) reaction, enabling expression of genes that mediate terminal differentiation [38]. However, in the presence of EZH2 mutation, suppression of GC exit genes and checkpoints persists, resulting in hyperplasia, and presence of other oncogene hits enables transformation to GCB-type DLBCL [39]. Accordingly, EZH2 selective inhibition leads to growth inhibition, differentiation, and apoptosis of DLBCL cells [39, 40]. In 2013, a phase I/II trial investigated the safety and efficacy of the first-in-class EZH2 inhibitor tazemetostat in 165 R/R DLBCL and FL patients. EZH2 mutation predicted response to treatment with ORR of 40% and 63% in patients with EZH2 mutant DLBCL and FL, respectively. On the contrary, ORR was 18% and 28% in patients with EZH2 wild-type DLBCL and FL, respectively. Grade ≥ 3 AEs were reported in 18% of patients, and the most common toxicities across all grades were nausea, thrombocytopenia, cough, diarrhea, fatigue, and weakness [41]. The FDA granted fast track designation for the investigation of tazemetostat for the treatment of patients with R/R DLBCL whose tumors carry an EZH2 activating mutation [42]. However, 3 months after approval, FDA imposed a partial clinical hold due to development of a secondary T cell lymphoblastic lymphoma in a patient enrolled in a phase I pediatric study (NCT02601937). Furthermore, FDA stopped development of tezemetostat monotherapy or in combination with prednisolone for DLBCL patients irrespective of EZH2 mutational status since the paucity of response. Currently, tezemetostat is under investigation in combination with other drugs such as atezolizumab in R/R DLBCL (NCT02220842) and R-CHOP (Epi-RCHOP) as a first-line treatment for newly diagnosed DLBCL patients (NCT02889523) [43].

Checkpoint Inhibitors

Checkpoint inhibitors have showed disappointing results in NHL as opposed to Hodgkin's lymphomas probably because only 27% of patients have programmed death ligand 1 (PD-L1) gene alterations. In an effort to enhance its efficacy, several combination approaches have been explored (NCT02362035, NCT03401853, NCT02950220, NCT02446457, NCT02729896). More recently, durvalumab, a PD-L1 inhibitor, was prospectively combined with either R-CHOP or R^2-CHOP in patients with previously untreated, high-risk DLBCL [44]. However, since previous studies showed significant toxicity when patients were treated with lenalidomide in combination with a checkpoint inhibitor, the FDA put clinical holds on the study arm combing durvalumab and R^2-CHOP. The ORR reported with durvalumab plus R-CHOP exceeded 50%. This finding is encouraging, particularly when considering that approximately one third of patients in the study had DHL or triple-hit lymphomas (THLs). Two-thirds of the patients in the study were able to receive consolidation therapy with durvalumab and were progression free a year after treatment. R-CHOP plus durvalumab might represent an advance for patients who are difficult to treat, particularly those with DHL or THL. A next step might be to evaluate this regimen in a randomized trial.

Maintenance Therapy

Previously, it has been showed that maintenance rituximab does not have a significant role in patients with DLBCL who achieved a first remission after frontline treatment with R-CHOP chemotherapy [45]. This earlier observation was recently confirmed in the randomized phase III trial performed by the Haemato Oncology Foundation for Adults in the Netherlands (HOVON) and the Nordic Lymphoma Group. For the first 4 cycles, the trial compared standard R-CHOP vs an R-CHOP regimen that used an intensified dose of rituximab. Patients in first remission entered the phase III portion of the trial and were randomly assigned to treatment with rituximab maintenance or observation. A previous report of this trial focused on whether the intensive rituximab regimen improved outcomes. The analysis identified no differences in the rates of CR and PFS with intensification of rituximab plus CHOP vs standard R-CHOP [46]. The presentation at the 2019 ASCO meeting provided data for the maintenance phase [47]. Patients received rituximab every 8 weeks for 2 years or underwent observation. The median follow-up was an appropriate duration of almost 80 months. The analysis found no statistically significant difference in the rate of 5-year disease-free survival between the 2 different arms, at 79% for rituximab maintenance vs 74% for observation. The hazard ratio was 0.83, and the confidence interval crossed 1. Not surprisingly, there was also no significant difference in the secondary endpoint of overall survival [47]. The results of this study provide further confirmation that rituximab maintenance has little to no additional benefit for patients with DLBCL who achieved a first complete remission after standard R-CHOP chemoimmunotherapy. Importantly, the majority of patients will be cured with standard R-CHOP chemoimmunotherapy, and there is a limited role in 2019 for maintenance rituximab in these patients.

Immunotherapy

The last decade has seen a revolutionary development of immunotherapy in B cell lymphomas. Cellular therapy with chimeric antigen receptor T cell therapy (CAR T) plays an increasingly important and evolving rule. Apheresed autologous T cells are genetically modified with cloned DNA plasmids carrying a gamma retroviral or lentiviral recombinant vector as well as genes expressing a chimeric T cell receptor targeting a cell surface antigen of interest. Anti-CD19-directed CAR T cells have been developed for R/R DLBCL, and two different

products, axicabtagene ciloleucel (axi-cel) and tisagenlecleucel (CTL019), have been approved from FDA and EMA for treatment of R/R DLBCL after two prior lines of systemic therapy.

Axicabtagene Ciloleucel (Yescarta)

Axi-cel contains a CD28 costimulatory domain in addition to a CD3 zeta domain. The ZUMA-1 is a phase I/II trial that evaluated axi-cel in patients with R/R DLBCL, primary mediastinal B cell lymphoma, or transformed FL [48]. After a median follow-up of 15.4 months, the investigator-assessed ORR was 82% with 54% of patients achieving a CR, and among 77 DLBCL patients, 49% were in CR. Notably, higher CAR T cell levels in blood were associated with response. Durable responses lasting longer than 1 year were observed across all subgroups, including age, refractory status, disease stage, and IPI score. The median DOR was 11.1 months for the entire study population (95% CI 3.9 months to not reached) and not reached for patients who archived a CR. The median PFS was 5.8 months (95% CI 3.3 months to not reached). The median OS was not reached, and the estimated 18-month OS was 52%. The most common AE of grade ≥ 3 during treatment was myelosuppression [neutropenia (78%), anemia (43%), and thrombocytopenia (38%)]. Grade ≥ 3 cytokine release syndrome (CRS) and neurologic events occurred in 13% and 28% of the patients, respectively. Three of the patients died during treatment [48]. Despite the high response rate, approximately 60% of patients relapse or progress after axi-cel. A post hoc analysis was done to evaluate protein expression of target antigen CD19 as well as other B cell lineage markers, including CD20, PAX5, CD79a, and CD22, in the tumor samples. Overall, 82 patients had tumor samples available for immunohistochemistry (IHC) analysis before treatment and 18 patients after disease relapse. Approximately one third of tumor samples after disease relapse had a loss of CD19 expression while the other B cell lineage markers remained expressed [49]. Antigen escape post–axi-cel may be mediated by selection of tumor cells with lower CD19 expression, or of tumor cells expressing alternate CD19 splicing variants. In particular, the alternative splicing events at baseline and relapse were found significantly different ($p < 0.05$). These splicing events likely led to the loss of the CAR-binding epitope, suggesting the need of novel strategies to improve efficacy of anti-CD19 CAR T cells through cotargeting or sequential targeting of alternate B cell antigens. [49]

Tisagenlecleucel (Kymriah)

Tisagenlecleucel (CTL019) is a CAR T cell consisting of a CD28 antigen-binding domain, a 4-1BB costimulatory domain, and a CD3 zeta signaling domain. The phase II JULIET trial is a single-arm, open-label, global study evaluating tisagenlecleucel in patients with R/R DLBCL who were ineligible for or had failed autologous stem cell transplant [50]. A total of 93 patients received a CAR T cell infusion and were evaluated for response. At a median follow-up of 26 months, the median DOR was not reached for patients in the main cohort. The ORR was 52% (95% CI 41–62) with a CR rate of 40% and a PR of 12%. Response rates were consistent across prognostic groups. A conversion from a partial to complete response 1 month after infusion occurred in 54% of the patients. Among the 35 patients who were in remission at 3 months, the probability to remain in remission at 12 months was 81% (95% CI 63–91). The median DOR has not been reached (95% CI 10 months to not reached) with 79% (95% CI 60–89) and 65% (95% CI 49–78) of patients who were in CR and PR remaining relapse-free at 12 months from response, respectively. The median PFS has not been reached for patients in CR. The median OS was 12 months (95% CI 7 months to not reached). Occurrences of CRS and neurological AEs were consistent with previous findings and the median time to onset was 3 and 6 days, respectively. CRS of any grade was experienced by 58% of patients, 22% of whom were grade 3/4. Twenty-one percent experienced any-grade neurological AEs and 12% experienced grade 3/4 [50]. Interestingly, there was a correlation between neurotoxicity and CRS. Eighty-three percent of patient who experienced any-grade neurotoxicity also developed CRS. Sixty-two percent of patients with severe neurotoxicity also developed severe CRS. Of the 49 patients who did not have CRS, only 4 had any-grade neurotoxicity. The highest serum biomarker profiles post-infusion appeared to associate with patients with severe CRS who were also non-responders [51].

Lisocabtagene Maraleucel

Lisocabtagene maraleucel (liso-cell), also known as JCAR017, is a unique CD-19-directed CAR T cell product which uses the 4-1BB costimulatory domain and CD3 zeta signal. When patient cells are collected, they are separated in their CD4 and CD8 components. The two cell types are separately transduced with a lentivirus vector, expanded, and then administrated to the patient in a 1:1 ratio, allowing the administration of a fixed, precise dose of liso-cells to each patient. The phase I TRANSCEND NHL 001 trial (NCT02631044) demonstrated a durable clinical benefit of liso-cells in patients with R/R DLBCL [52]. Among the 342 patients who underwent leukapheresis, 268 were infused with liso-cel at 1 of 3 dose levels (50×10^6, 100×10^6, or 150×10^6 CAR T cells). Since the outcomes among the 3 dose levels were similar, the data were pooled. Overall, 73% of patients responded and 53% had a CR. At a follow-up of 10.8 months, patients had a median DOR of 13.3 months (95% CI 8.2–not reached), and for patients who achieved a CR, the median DOR has not yet been reached. Patients had a median PFS of 6.8 months (95% CI 3.3–11.8) and a median OS of 19.9 months (95% CI 10.9–not reached). Grade ≥ 3 treatment-related AEs were seen

in 79% of patients, and the events were mostly cytopenias. CRS of any grade was seen in 42% of patients, 2% of whom had grade ≥ 3 CRS. In addition, 30% of patients had neurological AEs of any grade, 10% of whom had grade ≥ 3. A total of 4 patients died from AEs that were determined to be related to treatment with liso-cel and lymphodepletion [52]. Longer-term follow-up from the TRANSCEND study has showed that liso-cel resulted in a rapid, high rate of durable CRs with low incidence of severe CRS and neurologic events [52].

Polatuzumab Vedotin

Recently, the CD79 antibody-drug conjugate polatuzumab-vedotin associated with rituximab has emerged as effective therapeutic option in R/R DLBCL and has been granted an accelerated FDA approval [53]. However, also in this case, complete response rate was modest (21% and 45% in DLBCL and FL, respectively) [53]. To improve the cure rate in DLBCL, R-polatuzumab has been successfully combined with bendamustine, which doubled CR rate and median DOR of 8.8 months [54•]. However, bendamustine is not a highly active drug for R/R DLBCL and often induces severe and prolonged lymphopenia involving both T and B cells and hypogammaglobulinemia, increasing risk of infection and potentially hampering immune response against tumor [55, 56]. Early phase studies of polatuzumab-vedotin with lenalidomide and obinutuzumab [Pola-G-Len, NCT02600897], or lenalidomide, obinutuzumab, and venetoclax [NCT02611323] are ongoing in R/R DLBCL. Preliminary results from the phase I trial investigating the Pola-G-Len regimen showed an ORR of 76% with a CR rate of 65%. At a median follow-up of 11.27 months, median PFS was not reached. However, there was a remarkable toxicity with 79% of patients experiencing grade 3–4 AEs (neutropenia 50%, thrombocytopenia 23%, infection 16%), which led to a dose reduction or interruption of any drug in 34% and 73% of patients, respectively [57]. In frontline treatment of DLBCL, polatuzumab-vedotin is being evaluated as a replacement for vincristine within the R-CHOP regimen to avoid overlapping risk of neuropathy. The POLARIX study (NCT03274491) is the ongoing, international, randomized, double-blind, placebo-controlled, phase 3 study investigating polatuzumab-vedotin + R-CHP in untreated DLBCL [58].

MOR208

MOR208 is an Fc-enhanced monoclonal antibody against CD19, which leads to potentiation of antibody-dependent cell-mediated toxicity and phagocytosis, as well as direct cytotoxicity.

Lenalidomide showed highly activity when combined with MOR208, in a single-arm, phase II study of patients with R/R DLBCL [59]. The trial enrolled 80 patients, one third of who was rituximab-refractory. The regimen found 60% of responses among patients refractory to rituximab with PFS of approximately 1 year [59]. This can provide an opportunity to overcome rituximab resistance and improve response rate. And it might also act as a bridge to allow a more definitive treatment—perhaps cellular therapy—to be implemented at a later time.

Blinatumomab

Blinotumomab is a bispecific T cell engager (BiTE) antibody construct that binds to both CD3 on T cells and CD19 on B cells by 2 linked single-chain variable antibody fragments. T cells and B cells are brought together, allowing T cells to recognize and target malignant B cells, resulting in tumor cell apoptosis [60]. The phase II study in heavily pretreated R/R DLBCL reported a 43% ORR after 1 cycle of therapy with a 19% CR. Recently, the interim analysis of a phase II study (NCT03023878) assessing the efficacy of blinotumomab after first-line R-chemotherapy (R-CHOP, R-DA-EPOCH, or R-CHOEP) for patient with newly diagnosed, high-risk DLBCL was reported. Of 47 patients enrolled, 17 (36%) discontinued R-chemotherapy run-in and 30 (64%) complete the run-in. After blinotumomab, the ORR was 89% (25/28 patients; 95% CI 72–98). Four patients with no metabolic response before blinotumomab had objective response after blinotumomab treatment. Nine of 13 (69%) patients during R-chemotherapy were minimal residual disease (MRD) positive, all of whom converted to MRD negative after blinotumomab treatment. At a median follow-up of 8.6 months, twenty-six (93%) patients were still alive. Eleven (39%) patients have grade ≥ 3 AEs including neurologic events (11%), neutropenia, febrile neutropenia (14%), and infection (11%) and two patients had to discontinue treatment. No patients had grade ≥ 3 CRS [61]. These promising results suggest a rule for blinotumomab in patients with newly diagnosed disease. Currently, blinotumomab is also being evaluated as consolidation of autologous stem cell transplant (NCT03072771) and in combination with pembrolizumab (NCT03340766) in R/R DLBCL.

Mosunetuzumab

Mosunetuzumab is a bispecific monoclonal antibody that induces crosslinks between the CD3 component of the T cell receptor and the B cell surface antigen CD20. In an ongoing phase I/IIb study (NCT02500407), mosunetuzumab has showed antitumor activity and good tolerability in patients with heavily pretreated R/R NHL [62, 63]. This interim analysis included 270 patients with R/R NHL in the dose-escalation cohort of the study, including 85 patients with indolent NHL (e.g., mostly FL) and 180 patients with aggressive NHL (e.g., mostly DLBCL). Patients achieving a CR

discontinued treatment after 8 cycles, while a maximum of 17 cycles of mosunetuzumab was administered to those with a best response of PR or stable disease. In the overall group of 67 patients with indolent NHL who were evaluable for efficacy, the ORR was 62.7% and the CR rate was 43.3%, whereas in the corresponding group of 124 patients with aggressive NHL, the respective rates were 37.1% and 19.4%. Also notable was the durability of the CRs to mosunetuzumab—82.8% of patients with indolent NHL and 70.8% of patients with aggressive NHL who achieved a CR maintained this CR at a median follow-up period of up to 26 and 16 months off treatment, respectively. A patient subgroup of particular interest was comprised of those who had previously received CAR T therapy. Eighteen of the 30 patients in this subgroup were eligible for the efficacy analysis, which showed an ORR of 38.9% and a CR rate of 22.2%. Notably, approximately three-quarters of these patients were refractory to CAR T therapy [62•]. Regarding the safety of mosunetuzumab in the overall study population, grade 3/4 neutropenia occurred in 21.8% of patients, and a single grade 5 event of pneumonia occurred in a non-neutropenic patient. CRS occurred at a frequency 28.9%, although most of these events were classified as grade 1/2, with grade 3 CRS in 1.1% of patients, and most CRS events occurring during cycle 1 of treatment. Tocilizumab was administered to only 8 patients with CRS (3%) [63]. Dose optimization of mosunetuzumab is still ongoing in this study. Given the promising results, a phase I/II trial is investigating mosunetuzumab following first-line immunochemotherapy (NCT03677154) in newly diagnosed DLBCL.

Conclusions

In the last years, the genomic era has ushered in the possibility of using precision guided therapy, in part based on targeting genes with somatic mutations. Hence, a top priority in DLBCL research is to understand the molecular perturbation induced by mutant alleles so that precision-guided therapy regimens can be developed. Such precision-targeted therapies will ultimately reduce the need for chemotherapy, induce fewer adverse events, and likely enhance the cure rate for these patients. Although precision medicine and immunotherapy have led to advances in treatment of DLBCL, we are not yet able to overcome the barriers of inadequate response to them. This will require further exploration in future studies. In addition, the two new genetic classifications have paved the way to redefine therapeutic paradigm in DLBCL and develop mechanism-based combinatorial regimens specifically tailored for genetically defined subgroups.

Compliance with Ethical Standards

Conflict of Interest Patrizia Mondello declares that she has no conflict of interest.

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