Clinical Updates: Diffuse large B cell lymphoma (DLBCL) Pharmacotherapy

Atis Barzdins, MD

Hematologist and Medical Oncologist

Pacific Medical Centers

Seattle, WA

Objective

- Brief review of the diagnosis of Diffuse large B cell lymphoma (DLBCL) from medical oncologist's viewpoint
- Know the preferred induction regimens (NCCN guidelines)
- Become familiar with the wide spectrum of salvage treatments

Introduction to Diffuse large B cell lymphoma (DLBCL)

- Definition: DLBCL is an aggressive form of non-Hodgkin lymphoma characterized by large B cells in the lymph nodes, spleen, liver, bone marrow, or other organs.
- Epidemiology: Most common type of non-Hodgkin lymphoma, accounting for about 30-40% of cases. Incidence: Approximately 7 cases per 100,000 people annually.

Lymphoma Staging
(Lugano classification – simplified)

- Limited
  - Stage I — One node or a group of adjacent nodes
  - Stage II — Two or more nodal groups on the same side of diaphragm
- Advanced
  - Stage III — Nodes on both sides of diaphragm (including spleen)
  - Stage IV — Additional noncontiguous extralymphatic involvement

Eastern Cooperative Oncology Group (ECOG) performance status

0	Fully active, no restrictions
1	Strenuous physical activity restricted, fully ambulatory and able to carry out light work
2	Capable of all self-care but unable to carry out any work activities. Up and about >50% of waking hours
3	Capable only limited self-care, confined to bed or chair >50% of waking hours
4	Completely disabled; cannot carry out any self-care; totally confined to bed or chair

International Prognostic Index

- All patients – 1 point each:
  - Age >60 years
  - Serum LDH > normal
  - Performance status 2–4
  - Stage III or IV
  - Extranodal involvement >1 site
- International Index:
  - Low: 0 or 1
  - Low-intermediate: 2
  - High-intermediate: 3
  - High: 4 or 5

Traditional Treatment Approaches

- CHOP Chemotherapy: Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone.
- R-CHOP: Addition of Rituximab, a monoclonal antibody targeting CD20 on B cells.
- Stem Cell Transplantation: Used in relapsed or refractory cases.

POLARIX trial

- Clinical problem:
  - Up to 40% of patients treated with R-CHOP will have refractory disease or relapse after an initial response
  - Use of polatuzumab vedotin – an antibody–drug conjugate targeting CD79b, expressed on the surface of malignant B cells – could improve outcomes in DLBCL
- Double-blind, placebo-controlled, international phase 3 trial
  - Evaluated a modified regimen of R-CHOP (pola-R-CHP), in which vincristine was replaced with polatuzumab vedotin, as compared with standard R-CHOP, in patients with previously untreated intermediate-risk or high-risk DLBCL.

N Engl J Med. 2022;386(4):351. Epub 2021 Dec 14.

POLARIX trial: Intervention

- 879 patients were assigned to six 21-day cycles of pola-R-CHP or R-CHOP, followed by two cycles of rituximab monotherapy
- Patients had a baseline International Prognostic Index (IPI) score between 2 and 5
- patients received either intravenous **polatuzumab vedotin at a dose of 1.8 mg per kilogram of body weight** (pola-R-CHP group) or **intravenous vincristine at a dose of 1.4 mg per square meter of body-surface area** (maximum of 2 mg) (R-CHOP group)
- Standard doses of rituximab, cyclophosphamide, doxorubicin, prednisone
- The primary end point was investigator-assessed progression-free survival. Secondary end points included overall survival and safety

POLARIX trial: Results

- After a median follow-up of 28.2 months, the percentage of patients surviving without progression was significantly higher in the pola-R-CHP group than in the R-CHOP group (**76.7%** [95% confidence interval (CI), 72.7 to 80.8] vs. **70.2%** [95% CI, 65.8 to 74.6] at 2 years
- Overall survival at 2 years did not differ significantly between the groups (**88.7%** [95% CI, 85.7 to 91.6] in the pola-R-CHP group and **88.6%** [95% CI, 85.6 to 91.6] in the R-CHOP group.
- The safety profile was similar in the two groups.

POLARIX trial: Conclusions

- Among patients with previously untreated intermediate-risk or high-risk DLBCL, the risk of disease progression, relapse, or death was lower among those who received pola-R-CHP than among those who received R-CHOP

NCCN guidelines: Preferred first line regimens

- R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (category 1)
- Pola-R-CHP (polatuzumab vedotin, rituximab, cyclophosphamide, doxorubicin, prednisone) (IPI ≥2 in extensive disease or stage modified IPI>1 in limited disease) (category 1)

New treatments for refractory or relapsed disease

- Chimeric antigen receptor-T (CAR-T) cell therapy
- Bispecific antibody therapy
  - Glofitamab
  - Epcoritamab
- Other antibody-based therapies
  - Tafasitamab
  - Polatuzumab/bendamustine/rituximab
  - Loncastuximab
- Other treatments
  - Selinexor
  - Lenalidomide

Chimeric antigen receptor-T (CAR-T) cell therapy

- Immunotherapy that directs T cells against the lymphoma by ex vivo transfection of the patient's own T lymphocytes, using a gene that encodes a CAR.
- The manufacturing process is complex and expensive, administration is limited to qualified institutions, and the preferred product varies among institutions.
- Commercially available CD19-directed CAR-T cell agents are:
  - Axicabtagene ciloleucel
  - Lisocabtagene maraleucel
  - Tisagenlecleucel

Chimeric antigen receptor-T (CAR-T) cell therapy: Toxicities

- Cytokine release syndrome (CRS)
- Immune effector cell-associated neurotoxicity syndrome (ICANS)
- Other adverse events
  - hypersensitivity reactions,
  - serious infections,
  - prolonged cytopenias,
  - hypogammaglobulinemia,
  - second malignancies
  - tocilizumab (a humanized monoclonal antibody against the interleukin 6 receptor [IL-6R]) must be available for immediate administration.

Bispecific antibody therapy

- Bispecific antibodies link a CD3 antibody with another monoclonal antibody (eg, CD20) that targets the malignant B cells.
  - Glofitamab
  - Epcoritamab

Bispecific antibody therapy: Glofitamab

- Glofitamab is administered intravenously for a fixed duration of 12 cycles. Treatment begins with stepped-up doses of 2.5 and 10 mg, followed by 30 mg on day 1 of cycles 2 through 12.
- Associated with generally modest CRS, ICANS, tumor lysis syndrome, and infections.
- Outcomes: 52 percent overall response rate (ORR; including 39 percent complete response [CR]) and 37 percent 12-month progression-free survival

Bispecific antibody therapy: Epcoritamab

- Epcoritamab is subcutaneously administered given in 28-day cycles until disease progression or unacceptable toxicity
- Epcoritamab is administered once weekly as stepped-up doses in weeks 1 to 3 of cycle 1
- Prophylaxis for CRS: prednisolone, diphenhydramine and acetaminophen
- Toxicity: treatment is associated with CRS, ICANS, and cytopenias
- Outcomes: A multicenter study of 157 adults with refractory CD20-positive large B cell lymphoma and ≥2 prior lines of therapy (including anti-CD20 therapies) reported a 4.4-month median PFS and 63 percent ORR (including 39 percent CR); among patients with CR, the median PFS was not reached after >11 months

Other antibody-based therapies: Tafasitamab

- Tafasitamab is a humanized anti-CD19 monoclonal antibody.
- Tafasitamab should be administered with lenalidomide.
- Administration – Tafasitamab is given 12 mg/kg by intravenous infusion according to the following schedule in 28-day cycles:
  - Cycle 1: Days 1, 4, 8, 15, and 22
  - Cycles 2 and 3: Days 1, 8, 15, and 22
  - Cycle 4 and beyond: Days 1 and 15
  - Lenalidomide 25 mg by mouth on days 1 to 21 of each cycle is taken in combination with tafasitamab for a maximum of 12 cycles

Other antibody-based therapies: Polatuzumab/bendamustine/rituximab

- Polatuzumab vedotin 1.8 mg/kg over 90 minutes is given by intravenous infusion every 21 days for six cycles, in combination with bendamustine and rituximab. If the previous infusion was tolerated, subsequent infusions may be administered over 30 minutes
- Toxicity: Grade ≥3 AEs occurred in two-thirds of patients (mostly cytopenias and infections) and were fatal in 7 percent.
- Prescribing information includes warnings for peripheral neuropathy, infusion reactions, myelosuppression, serious and opportunistic infections, progressive multifocal leukoencephalopathy (PML), tumor lysis syndrome, hepatotoxicity, and fetal toxicity

Other antibody-based therapies: Loncastuximab

- Loncastuximab tesirine is a CD19-directed antibody-drug conjugate.
- Loncastuximab is given as an intravenous infusion over 30 minutes on day 1 of each three-week cycle:
  - 0.15 mg/kg for two cycles
  - 0.075 mg/kg for subsequent cycles
  - Dexamethasone prophylaxis should be given for three days, beginning day -1 (ie, the day before treatment).

Selinexor

- Selinexor is an orally available selective inhibitor of nuclear export
- Selinexor was associated with an objective response in approximately one-quarter of highly selected patients, but it is associated with significant toxicity
- In a multicenter study, 127 heavily pretreated patients received selinexor 60 mg by mouth on days 1 and 3 each week and achieved 28 percent ORR, including 12 percent CR
- The most common grade ≥3 AEs were thrombocytopenia (46 percent), neutropenia (24 percent), anemia (22 percent), fatigue (11 percent), hyponatremia (8 percent), and nausea (6 percent). There were no treatment-related deaths, and AEs were generally reversible and manageable with dose modifications and supportive care.

Relapsed disease >12 mo

- Autologous HCT is recommended for patients who can tolerate it and achieve complete response [CR] or near-CR to salvage chemotherapy) rather than CAR-T cell therapy
- Preferred regimens (in alphabetical order)
  - DHA (dexamethasone, cytarabine) + platinum (carboplatin, cisplatin, or oxaliplatin) ± rituximab
  - GDP (gemcitabine, dexamethasone, cisplatin) ± rituximab or (gemcitabine, dexamethasone, carboplatin) ± rituximab
  - ICE (ifosfamide, carboplatin, etoposide) ± rituximab
- Other recommended regimens (in alphabetical order)
  - ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) ± rituximab
  - GemOx (gemcitabine, oxaliplatin) ± rituximab
  - MINE (mesna, ifosfamide, mitoxantrone, etoposide) ± rituximab

Second line therapy – no intention to transplant (NCCN guidelines)

- Preferred regimens (in alphabetical order)
  - CAR T-cell therapy (CD19-directed)k (if eligible)
  - Polatuzumab vedotin ± bendamustin ± rituximab
  - Tafasitamab + lenalidomide

Third and subsequent line therapy (NCCN)

- Preferred regimens: T-cell engager therapy
  - CAR T-cell therapy (preferred if not previously given)
  - Bispecific antibody therapy (only after at least two lines of systemic therapy; including patients with disease progression after transplant or CAR T-cell therapy) (in alphabetical order)
    - Epcoritamab
    - Glofitamab
- Other recommended regimens
  - Loncastuximab
  - Selinexor (including patients with disease progression after transplant or CAR T-cell therapy)

Conclusions

- Most patients with DLBCL can be cured with induction immunochemotherapy.
- According to NCCN guidelines, preferred induction regimens are:
  - R-CHOP - all patients
  - Pola-R-CHP for increased risk patients (IPI ≥2 in extensive disease or stage modified IPI>1 in limited disease)
- Treatment options for patients with relapsed or refractory DLBCL have significantly improved in the recent years.