LymphomaHub

DLBCL

Treatment strategies and prognostic tools

Cynthia Umukoro | Nov 14, 2016

Treatment strategies for Diffuse Large B-Cell Lymphoma (DLBCL) should be based on age, International Prognostic Index (IPI) and feasibility of dose-intensified approaches. A clinical trial should be recommended, if available.[1,2]

The standard treatment approach for DLBCL is cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) chemotherapy. Complete Response (CR) rates are 50% in those aged 65–75 years, but 40% in those aged >75 years.[1-3] Prospective randomized trials have looked at the use of alternative CHOP and etoposide and the role of anthracyclines in older patients receiving non-rituximab-containing regimens (CHOP14/CHOP21, CHOEP).[4]

There are no standard treatment options for young patients with high and high-intermediate risk DLBCL, and so these groups may benefit from participating in clinical trials. These patients can benefit from 6–8 cycles of CHOP with 8 doses of rituximab (R). Trials have been conducted to compare rituximab followed by high-dose chemotherapy and Autologous Stem Cell Transplantation (ASCT) *versus* R-chemotherapy alone, showing mixed results.[1] A Progression Free Survival (PFS) benefit has been seen in some trials but no advantage in Overall Survival (OS). R-ACVBP or rituximab, cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone (R-CHOEP) are also often used.[1] The role of interim Positron Emission Tomography (PET) analysis to select patients who could benefit from consolidative ASCT or radiotherapy is under evaluation.[5,6]

For patients aged 60–80 years old, combination therapy with CHOP plus 8 doses of rituximab is the current standard of care.[7] Radiotherapy does not confer therapeutic benefit to these patients.[8] R-CHOP given every 14 days did not demonstrate a survival advantage over R-CHOP given every 21 days (R-CHOP-21)[9] and therefore RCHOP-21 is still the standard treatment for DLBCL. Extended rituximab exposure has been shown to improve outcomes in elderly patients with poor prognosis, without increasing toxicity.[10]

For fit patients over the age of 80, a combination of rituximab with attenuated chemotherapy such as R-miniCHOP is recommended and can induce a complete response and long survival. For frail patients or those with cardiac dysfunction, substitution of doxorubicin with gemcitabine, etoposide or liposomal doxorubicin, or even omission of doxorubicin can be considered from the beginning or after a few cycles.[1]

It should be noted that Central Nervous System (CNS) relapse occurs in about 5% of DLBCL patients during the disease course. It has been shown that patients with testicular or kidney/adrenal involvement and patients with more than one extranodal site are at high risk of CNS relapse.[11,12]

Despite the advances in treatment of DLBCL, 30% of patients will eventually relapse. In addition to initial prognostic factors, the nature of previous treatments and time from initial treatment are very important.[1]

In patients aged 65–70 years with a good prognostic score and no major organ dysfunction, salvage regimens with rituximab and chemotherapy followed, in responding patients, by High-Dose Chemotherapy (HDCT) and ASCT are used.[1] Salvage regimens such as rituximab, cisplatin, cytarabine, dexamethasone (R-DHAP) and R-ICE have shown similar outcomes.[13] Rituximab gemcitabine, cisplatin and dexamethasone (R-GDP) has been shown to have similar efficacy but less toxicity than DHAP.[14]

ASCT remains a valid option in Relapsed/Refractory (R/R) DLBCL.[1] Allogeneic Transplantation (allo-SCT) may be an option for patients with refractory disease, early relapse or who relapse after ASCT.[1] Allo-SCT after ASCT as a tandem strategy provides promising results compared with ASCT alone in patients with relapsed DLBCL with one or more adverse prognostic features.[14] Rituximab, gemcitabine and oxaliplatin (R-GEMOX) regimen has been used in patients not suitable for HDCT.

In summary, therapy for difficult-to-treat NHLs has improved significantly over the past 30 years and there has been recognition of distinct subtypes that might require special treatment approaches. Rituximab-containing regimens have become the gold standard in treatment of DLBCL. Newer generations of monoclonal antibodies and other therapies that interfere with intrinsic tumor-related mechanisms of resistance are currently being evaluated.

References:

1. Tilly H. *et al.* Diffuse large B-cell lymphoma (DLBCL): ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015 Sep: 26 (suppl5);v116–25. doi: 10.1093/annonc/mdv304.
2. McKelvey E.M. *et al.* Hydroxyldaunomycin (Adriamycin) combination chemotherapy in malignant lymphoma. Cancer. 1976 Oct; 38(4):1484–93.
3. O'Reilly S.E. *et al.* Malignant lymphomas in the elderly. Clin Geriatr Med.1997; 13(2):251–263.
4. Connors J.M. & O'Reilly S.E. Treatment considerations in the elderly patient with lymphoma. Hematol Oncol Clin North Am. 1997 Oct; 11(5): 949–961.
5. Casasnovas R.O.*et al.* Final results of a randomized phase II GELA/LYSA study of rituximab plus ACVBP or CHOP, using a PET-driven consolidation strategy, in patients with high-risk diffuse B-cell lymphoma (DLBCL). J Clin Oncol. 2014; 32:5s; (suppl abstract 8503).
6. Sehn L.H. *et al.* Phase 2 trial of the interim PET scan-tailored therapy in patients with advanced stage diffuse large B-cell lymphoma (DLBCL) in British Colombia (BC). Blood. 2014; 124: 392.
7. Coiffier B. *et al.* Long-term outcome of patients in the LNH-98.5 trials, the first randomized study comparing rituximab-CHOP to standard CHOP chemotherapy in DLBCL patients: a study by the Groupe d'Etudes des Lymphomes de l'Adulte. Blood. 2010 Sep; 116(12):2040–45. doi: 10.1182/blood-2010-03-276246. Epub 2010 Jun 14.
8. Held G. *et al.* Role of radiotherapy to bulky disease in elderly patients with aggressive B-cell lymphoma. J Clin Oncol. 2014 Apr; 32(11): 1112–1118. doi: 10.1200/JCO.2013.51.4505. Epub 2014 Feb 3.
9. Delarue R. *et al.* Dose-dense rituximab-CHOP compared with standard rituximab-CHOP in elderly patients with diffuse large B-cell lymphoma (the LNH03-6B study): a randomized phase 3 trial. Lancet Oncol.2013 May; 14:525–533. doi: 10.1016/S1470-2045(13)70122-0. Epub 2013 Apr 9.
0. Pfreundschuh M. *et al.* Optimization of rituximab for the treatment of diffuse large B-cell lymphoma (II): extended rituximab exposure time in the SMARTE-R-CHOP-14 trial of the German High-Grade Non-Hodgkin Lymphoma Study Group. J Clin Oncol. 2014 Dec; 32:4127–33. doi: 10.1200/JCO.2013.54.6861. Epub 2014 Nov 17.
1. Kridel R. & Dietrich P.Y. Prevention of CNS relapse in diffuse large B-cell lymphoma. Lancet Oncol. 2011 Dec; 12(13): 1258–1266. doi: 10.1016/S1470-2045(11)70140-1. Epub 2011 Sep 18.

2. Savage K.J. *et al*. Validation of a prognostic model to assess the risk of CNS disease in patients with aggressive B-cell lymphoma. Blood 2014; 124:394.

3. Crump M. *et al*. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY. J Clin Oncol. 2014 Nov; 32(31):3490–3496. doi: 10.1200/JCO.2013.53.9593.

4. Crocchiolo R. *et al*. Autologous stem cell transplantation followed by allogeneic SCT provides promising results in patients with relapsed DLBCL and adverse prognostic features compared with ASCT alone. Blood. 2015; 126:2034.