EDITORIAL

New Approaches for Diffuse Large B cell Non Hodgkin Lymphoma Management Strategy

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Diffuse large B cell Non Hodgkin lymphoma (DLBCL) is the most frequent subtype, accounts for 30%–40% of cases. The disease is usually aggressive but there is high chance of cure with appropriate treatment lines.

For long time, R-CHOP kept as a classical treatment approach. It can achieve long-term disease control in nearly 90% of patients presenting with limited-stage and up to 60% of those presenting with advanced stages. It was first choice therapy that fit all patients with a significant cure rate, however; here was still one third patients who passed in refractory relapsed state.

Some patients had discovered to be less responsive than other with this course of treatment especially those elderly patients or presenting with high international prognostic index (IPI), and those originating from non germinal center (non GC) phenotype labeled as double hit or double expresser lymphoma. For which different approaches may require!

Ten to fifteen percent of newly diagnosed cases found to have MYC rearrangement, resulting in dysregulated cellular survival and proliferation, in addition to another approximately 50% expressing rearrangement of the anti-apoptotic proto-oncogene BCL2 and/or its transcription repressor BCL6 in case of double hit lymphoma.

These classification systems are now routinely used to identify subsets of patients with high-risk disease and poorer outcomes to up-front standard R-CHOP therapy.

Patient with relapsed state can still get cure in around 50% chance after receiving salvage chemotherapy and followed by autologous stem cell transplantation (ASCT) whenever responding, while those non responder or those had no access to ASCT for a reason or another, may continue palliative courses until recently.

Sixty percent may get relapse after ASCT where allogeneic stem cell transplantation can offer new chances.

Many centers are still applying these approaches for DLBCL patients, but the new advancement in understanding the role of cell of origin in state of disease gives further treatment plans as second line or even upfront therapy from the start; thus, recently discovered targeted chemoimmunotherapy have revolutionized treatment decision particularly in relapsed/ refractory (R/R) state as well as , the approach applying Chimeric antigen receptor T-cell (CAR T cell) therapy had transform disease treatment evolution and outcome.

Chimeric antigen receptor T-cells (CAR T) therapies are autologous genetically modified T cells formed by combining the antigen-binding site of an antibody with the intracellular domain of a T-cell activation receptor. The CAR gene is introduced into the T cell genome using a gamma retroviral or lentiviral vector. Upon encountering the surface antigen of interest in the target cell, the T-cell receptor's intracellular domain is directly stimulated independently of the HLA-complex.

Currently, there are 3 FDA-approved CAR-T cell products for the treatment of R/R DLBCL after ≥2 lines of systemic therapy: axicabtagene ciloleucel (axi-cel), tisagenlecleucel (tisa-cel), and lisocabtagene maraleucel (liso-cel).

They present an appreciable complete response rate with most common adverse effects including cytokine release syndrome (CRS) in around 42- 92% and neurological toxicities syndrome as immune effect or cell associated neurological syndrome (ICAN) in range of 20-67% with mild severity in most reports and don't reach to grade 3 toxicity.

The ZUMA-1 trial led to the approval of axi-cel with a reported overall response rate (ORR) of 83% and a completer response (CR) rate of 54%, with ongoing responses observed in 42% of patients.

The approval of tisa-cel was based on the JULIET trial reporting an ORR of 52% with a CR rate of 40%.

The approval of liso-cel was based on the phase 1 TRANSCEND NHL 001 trial in which an ORR of 73% and a CR in 53% of patients with heavily pretreated large B-cell lymphoma

Nevertheless, CAR T cell therapy is a third line but can give a durable response in 30-40% of patients.

Meanwhile novel therapies approved to be effective for those not accessed for CAR T cell option, these including Antibody-drug conjugates (ADCs) are complex molecules that selectively deliver cytotoxic agents to tumor cells by conjugation of a monoclonal antibody directed toward a target antigen expressed on the cancer cell surface via a chemical linker *polatuzumab vedotin* (PV), which is a CD 79b drug conjugate.

It had tried in combination with (bendamustin/rituximab) BR and gave an improve CR, PFS and OS according to phase II randomized trial in comparison with BR alone in R/R disease.

However PV had suggested to upgrade as upfront therapy according to (POLARIX study) where a switch standard of care for DLBCL from R-CHOP toward (pola R/G-CHP) as first line treatment as vincristine in R-CHOP replaced by PV and resulted a significant improvement in PFS ($P< 0.2$) when compared with standard R-CHOP over 24 months median follow up(76.7% Vs 70.2) and reduction 27% relative risk of progression , relapse, and death. Similarly EFS statistically improved ($P<0.2$) with comparable safety profile, while OS is not differ from R-CHOP.

Other chemoimmunotherapy included: *Tafasitamab*: a humanized monoclonal antibody against CD19 with Fc-enhanced direct cytotoxicity and enhanced antibody-dependent cell-mediated toxicity and phagocytosis, when combined with lenalidomide, an ORR and CR reach 60% and 43% respectively.

Selinexor is an oral selective inhibitor of exportin 1 (XPO1), a protein that is overexpressed in all types of malignant lymphoma, (DLBCL) and gives ORR 28% in heavily pretreatment cases.

Another development in treatment approaches considered Bispecific T-cell engager therapy (BiTEs): which are antibodies formed by two single-chain variable fragments, one of which binds to a tumor antigen and the other onto T cells (mostly CD3), thus; leads to T-cell mediated killing of tumor cells independent of MHC class I.

BiTEs, similarly to CAR T cells, can stimulate the secretion of cytokines and potentially modify the tumor microenvironment, thereby restoring effective anti-tumor immunity via CD20/CD3 like (*Mosunetuzumab,Glofitamab ,Epcoritamab*) with an accepted response rate in clinical trial but not yet approved for R/R DLBCL .

In conclusion: DLCBL is not a single disease genotype and phenotype that requires good understanding of the genetic and molecular landscape to improve upfront therapies options, particularly for high-risk patients.

Thereafter landscape for R/R DLBCL had changed with introduction of CAR T cell option for those non responding to salvage chemotherapy and not candidate to switch to ASCT or even those relapsed after ASCT .

However other questions that still to investigate like comparison between BiTEs and CAR T cell therapy to define which is more preferable and whether BiTEs can be incorporated into combination protocols or used as monotherapy only?

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