CAR T-cell therapy-transforming treatment of hematological malignancies

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Hematological malignancies are a significant cause of mortality and morbidity in all age groups. According to the Global Burden of Disease Cancer Collaboration, there were about one million incident cases of hematological malignancies worldwide in 2016.[1] In an analysis of NORDCAN database, it was observed that the 5-year survival rates during the period 1999–2003 for Hodgkin lymphoma, Non-Hodgkin lymphoma, acute leukemia, other leukemia, and multiple myeloma were 80, 50–60, 38–49, 60–73, and 28–41%, respectively.[2] The treatment of these blood cancers has seen rapid advances in modern medicine. However, mortality is still very high and globally, about half a million deaths were attributed to these malignancies in 2016 alone.[1] In some cancers, such as the relapsed/refractory B-cell precursor-ALL, the 5-year survival rate is only 10% with conventional treatment.[3]

Conventionally, chemotherapy has been the mainstay of treatment supported by radiation therapy, targeted therapy, or stem-cell transplantation resulting in improved outcomes. Novel treatment options that improve outcomes are under research worldwide. The chimeric antigen receptor T-cell therapy (CAR-T) is a promising novel anticancer treatment modality. A CAR-T therapy consists of infusion of engineered T-cells that express a chimeric antigen receptor on their cell membrane. *In-vivo*, CAR-T cells eliminate tumor cells with precision by interacting with the tumor-associated antigens (TAAs) on tumor cell surface independent of the expression of major histocompatibility complex.[4] CAR is a recombinant immunoreceptor composed of an extracellular binding domain (TAA-reactive antibody derived Single-chain variable fragments), a hinge region, a transmembrane domain, and one or more intracellular signaling domains (CD3ζchain).[5] Second-, third-, and fourth-generations of these receptors have costimulatory domains such as CD28 and/or 4-1BB which enhance auto-proliferation, cytokine secretion, apoptosis resistance, and *in-vivo* persistence. Fourth generation CARs have additional enzyme secreting properties which degrade extracellular matrix of solid tumours.[5]

The first FDA approved therapies, tisagenlecleucel followed by axicabtagene ciloleucel, are third generation anti-CD19 CAR T-cells indicated for treatment of refractory B-cell acute lymphoblastic leukemia (in children and young adults) and refractory diffuse large B-cell lymphoma (in adults), respectively. The approval was based on Phase II trials (ELIANA trial for tisagenlecleucel and ZUMA-1 trial for axicabtagene). An objective response rate of 81 and 82% was observed, respectively.[6,7] The success of these therapies has rekindled the hope for targeting other malignancies which have been hitherto refractory to treatment.

At present, CAR-T cell therapy targeting CD7/CD23/CD33/CD34/CD38/CD56/CD117/CD123/CD133/Mucl (for acute myeloid leukemia), CD19/CD20/CD22/EGFR (for chronic lymphocytic leukemia), CD30 (for Hodgkin lymphoma), and CD38/CD138 (for multiple myeloma) are in various stages of Phase I/II clinical trials (nearly 150). Despite the initial better outcomes, it is too early to predict the final picture. Serious adverse drug reaction (CRS-cytokine release syndrome and NT-neurotoxicity) leading to fatality has already been reported.[8] Moreover, concerns have been expressed about tumor relapse, genotoxicity, and autoimmunity as long-term consequences.[8] In the Phase 2 ELARA trial, tisagenlecleucel was found to be safe and effective in adult relapsed or refractory follicular lymphoma.[9] However, the BELINDA trial (Phase III trial) failed to show superiority to standard salvage therapy.[10] On an optimistic note, ZUMA-7 trial and TRANSFORM trial for axicabtagene in early relapsed or

refractory large B-cell lymphoma demonstrated improved survival and response outcomes compared to standard therapy.[11] A handful of Phase 3 trials are underway to test the efficacy and safety of the "revolutionary" drugs in the treatment of hematological malignancies. The acceptability of these "living drugs" in the future will depend on the results of these trials and beyond.

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