Development of Immune, cell and target therapy in lymphoid malignancies

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Novel agents and new drugs are developing along with advanced understanding biology in lymphoid neoplasm. The most well recognized tumorigenesis in lymphoid neoplasm is the B cell receptor (BCR) pathway. Many monoclonal antibodies target to B cell receptor are investigated.

Rituximab is the first anti-CD20 monoclonal antibody for human B cell lymphoid neoplasms and open the new area of target therapy. It's approval for chronic lymphoid leukemia (CLL), follicular lymphoma (FL), and diffuse large B cell lymphoma (DLBCL). Obinutuzumab, a latest anti-CD20 monoclonal antibody was proved to be more efficacious than rituximab in CLL and FL. Bruton's tyrosine kinase (BTK) is located at cytoplasm and transmits signal from BCR. Ibrutinib is a BTK inhibitor and demonstrates clinical benefit in CLL, mantle cell lymphoma (MCL), and Waldenstrom's macroglobulinemia (WM). Acalabrutinib is an irreversible second generation BTK blocker and is approval for relapse MCL.

The phosphoinositide 3-kinase (PI3K) pathway is a critical signal transduction, regulates cell proliferation and linked many oncogene and cell receptors. Idelaisib is the first approval BTK inhibitor and applies for relapse CLL and FL. Copanilisib is a pan-class PI3K inhibitor and demonstrated promising efficacy in both indolent and aggressive lymphomas. Anti-CD30 monoclonal antibody is applied for lymphoma expressing CD30, such as classical Hodgkin lymphoma (cHL) or anaplastic T cell lymphomas. Brentuximab is indicated for relapse or refractory CD 30 positive cHL.

However, Hodgkin lymphoma is characteristic with 9p24 amplification and increases PD-1 ligand expression. Nivolumab is a PD-1 inhibitor and the first immunotherapy applied for cHL. 66.3% response rate was noted in a phase II trial for cHL patients relapse from both autologous stem cell transplantation and brentuximab treatments. Pembrolizumab also demonstrates the clinical benefits for relapse/refractory cHL in KEYNOTE-87 study. Both nivolumab and pembrolizumab are approval by FDA for relapse or refractory cHL. Other check-point inhibitors, such as Atezolizumab and avelumab are going to be investigated.

Chimeric antigen receptor (CAR) modified T cell therapy gets success in refractory or relapse acute lymphoblastic leukemia. However, most CAR-T therapy in lymphoma is still under investigated. In a phase II ZUMA-1 study, KTE-C19

demonstrate objective response of 79% and complete remission of 52% for aggressively relapse or refractory non-hodgkin's lymphomas. Further studies investigations are developed.

In conclusion, with the advanced knowledge of immune system, tumorigenesis and biology, more and more novel agents and treatment modalities designed for lymphoid malignancies are anticipated.