Monoclonal Antibody-drug Conjugates GO and Inotuzumab Are Effective in Adult Acute Leukemia

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Abstract

On June 14-17, 2018, the 23rd EHA conference was held in Sweden-Stockholm. The heavy research in the blood field took place. The development of new drugs in the field of acute leukemia has progressed rapidly. Among them, antibody-drug conjugates(ADC) including Gemtuzumab Ozogamicin targeting CD33 and Inotuzumab targeting CD22 showed significant effects in adult acute myeloid leukemia and adult acute lymphoblastic leukemia, respectively.

Citation: Bella Smith Monoclonal Antibody-drug Conjugates GO and Inotuzumab Are Effective in Adult Acute Leukemia. **protocols.io**

dx.doi.org/10.17504/protocols.io.reid3ce

Published: 30 Jun 2018

Document

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In recent years, the following areas of adult acute myeloid leukemia (AML) have been approved for major drugs or made significant progress.

The first is a CD33 monoclonal antibody ADC drug called calicheamicins that has been approved by the US FDA for the treatment of AML, called Gemtuzumab Ozogamicin (GO). For patients with relapsed/refractory (R/R) and part of newly diagnosed AML, GO has achieved good results in both the induction and consolidation phases.

Also as a targeted drug, the marketed FLT3 inhibitor Midostaurin (Metostatin) is the first FLT3 target inhibitor approved by the US FDA for the treatment of AML. For patients with FLM3 ITD mutation-positive AML, midazolam combined with conventional chemotherapy can significantly improve event-free survival (EFS) and overall survival (OS).

IDH1 and IDH2 are common gene mutations in AML and are potential therapeutic targets. Enasidenib, an IDH2 inhibitor, and Ivosidenib, an IDH1 inhibitor, have been approved by the US FDA for the treatment of patients with AML. In addition to the above targeted inhibitors, another exciting drug is a combination of liposomal daunorubicin and cytarabine (Ara-C). Compared to traditional daunorubicin combined with Ara-C, its advantages lie in better targeting of leukemia cells, improved efficacy, and reduced cardiotoxicity, especially for elderly AML patients who cannot tolerate strong chemotherapy.

Other drugs that have broad therapeutic potential in the AML field are the BCL-2 inhibitor ABT-199. For

elderly patients with AML who are unable to tolerate chemotherapy, they are given a combination of low-dose Ara-C or a combination of epigenetic control agents such as alzheimer's with a higher rate of complete remission (CR). Further research results are worth looking forward to, this drug is expected to improve the long-term survival rate of AML patients.

The prognosis of patients with acute myeloid leukemia (AML) in adults is more heterogeneous and stratified according to the degree of risk. The prognosis of each group is quite different. The long-term survival rate of medium-risk patients is about 40% to 50%, and the long-term survival rate of high-risk patients is less than 20%. The survival needs of AML patients are far from being satisfied. Among the above-mentioned new drugs in the AML field, Gemtuzumab Ozogamicin (GO) is a representative of a CD33 monoclonal antibody conjugates. CD33 is a myeloid cell differentiation antigen that is expressed in most leukemia cells in AML patients, so almost all patients with AML can receive this antibody treatment. After years of development, the safety of this drug has been further verified and guaranteed by further optimizing the use strategy, exploring the use of methods and doses, and mastering the usage patterns. In 2017, this drug was re-approved for listing. In terms of efficacy, GO can significantly increase the long-term survival rate of patients in the intermediate-risk group, and can significantly improve the remission rate in patients with R/R AML.

Therefore, for the AML patients in China, the use of GO in the future will certainly further meet their treatment needs. We should further explore how to better use this drug to further eliminate minimal residual disease (MRD), improve remission rate, prolong recurrence-free time, and prolong OS.

At present, a more prominent problem in the treatment of adult acute lymphoblastic leukemia (ALL) is the higher recurrence rate after remission. The strategies for rescue treatment after recurrence are mainly the following three types: 1. using large doses of cytarabine; 2. using large doses of methotrexate; 3. using traditional VDP (vincristine + daunorubicin + Glucocorticoids are the chemotherapy regimens for the skeleton. However, in general, the efficacy of these three treatment strategies is similar, and the overall feature is the low rate of remission, which seriously restricts the therapeutic efficacy and long-term survival of patients with adult ALL after recurrence. Inotuzumab ozogamicin is a CD22 monoclonal antibody-conjugated drug. In phase III clinical trials, Inotuzumab ozogamicin treatment significantly increased the CR rate by up to 80% compared with the standard chemotherapy group. Patients with CR who received CD22 antibody therapy had significantly longer progression-free survival (PFS). The overall survival of the patient was significa ntly improved. Based on the above findings, the US FDA has now approved its use for the treatment of R/R B-ALL.

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