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Novel Immunotherapy Approaches in AML: Focus on Monoclonal Antibodies

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Abstract

Monoclonal antibody (mAb)-based therapies have become an important modality for cancer treatment but have had limited success to date in acute myeloid leukemia (AML). Identification of new antigenic targets and antibody engineering techniques may overcome the modest anti-leukemic effects seen with most native antibodies studied previously in AML. Advances in bispecific immune-engaging antibody technology may improve the pharmacology of these agents, and the safety and efficacy of antibody-drug conjugates (ADCs) may be enhanced by better cytotoxic payloads and chemical linkers. Radioimmunotherapy with β particle-emitting isotopes may play in role as conditioning for hematopoietic cell transplantation (HCT), while short-ranged α particle-emitters may allow for more efficient leukemia cell killing with less bystander effects.

Introduction

Acute myeloid leukemia (AML) is a heterogeneous group of malignancies characterized by impaired differentiation and increased proliferation of early hematopoietic cells. Although there have been modest improvements in the outcomes of AML patients in recent years, treatment results remain disappointing, particularly for older individuals.[1] Monoclonal antibody (mAb)-based therapies have become an integral part of cancer treatment, and leukemia is well-suited to this approach because of the accessibility of malignant cells in blood and bone marrow. Until recently, most studies focused on CD33, but a number of alternative antigens are now under investigation. We will review potential therapeutic targets and highlight several mAb-based modalities, including unconjugated antibodies, bispecific immune-engaging antibodies, antibody-drug conjugates (ADCs), and radioimmunotherapy. Other approaches, such as cell-based therapies and immune checkpoint inhibition, are reviewed elsewhere.[2,3]

Target Antigens for Immunotherapy of AML

Promising target antigens for AML immunotherapy are summarized in Table 1. CD33, a member of the sialic-acid-binding, immunoglobulin-like lectin family, is a 67-kDa transmembrane glycoprotein. It is expressed on most myeloid and monocytic leukemia cells in addition to myelomonocytic and erythroid progenitors but is not seen on pluripotent stem cells, granulocytes, lymphoid cells, or non-hematopoietic tissues. Phosphorylation of tyrosine residues on the cytoplasmic tail of CD33 can recruit and activate the tyrosine phosphatases SHP-1 and SHP-2, suggesting that CD33 functions as an inhibitory receptor.[4] CD123, a 75-kDa type-I membrane protein, is the alpha subunit of the interleukin-3 receptor. It is

expressed on monocytes, B cells, megakaryocytes, plasmacytoid dendritic cells, and hematopoietic stem and progenitor cells. Overexpression of CD123 can promote increased cell survival and proliferation[5] and is associated with lower remission and survival rates.[6] CD45 is a protein tyrosine phosphatase expressed on all hematopoietic cells except mature red blood cells and platelets.[7] CD47, a 50-kDa glycoprotein that belongs to the immunoglobulin superfamily, can inhibit phagocytosis through interaction with signal regulatory protein-α (SIRPα) on macrophages. CD47 is found on leukemia stem cells (LSCs), and overexpression in AML has been associated with an adverse prognosis.[8] C-type lectin-like molecule 1 (CLL1), is seen on LSCs as well as myeloid progenitors, peripheral blood monocytes, dendritic cells, and granulocytes; however, it is not expressed by normal hematopoietic stem cells.[9]

Table 1. Selected Potential Target Antigens for Immunotherapy of AML

Antigen	Advantages	Disadvantages
CD33[4]	• Expressed on most myeloid blasts • Low or no expression on HSCs • Internalization can optimize drug or radioisotope delivery	• Expressed on normal myeloid progenitors • Internalization can limit effector function • Relatively low copy numbers on leukemic blasts (~10,000/cell)
CD123[5,6]	• Expressed on myeloid blasts and LSCs • Low or no expression on HSCs • Associated with increased survival and proliferation • Associated with poor prognosis in AML	• Expressed on myeloid progenitors and other normal hematopoietic cells
CD45[7]	• Not expressed by non-hematopoietic tissues • Not internalized	• Broad expression necessitates HCT
CD47[8]	• Universal target in human cancers • Overexpressed on LSCs compared to normal hematopoietic cells	• Expressed on majority of normal tissues
CLL1[9]	• Expressed by most myeloid blasts and LSCs • Not expressed by normal HSCs	• Expressed on monocytes, dendritic cells and granulocytes • Relatively low copy numbers • Internalization can limit effector function

Abbreviations: HSC = hematopoietic stem cell; LSC = leukemia stem cell; HCT = hematopoietic cell transplantation.

Unconjugated Antibody Therapy

Lintuzumab is a humanized mAb with activity against minimal residual disease (MRD) in acute promyelocytic leukemia[10] and modest effects against relapsed and refractory (R/R) AML.[11] The role of lintuzumab in combination with chemotherapy was examined in two randomized trials. A phase III trial showed no difference in response rates or overall survival (OS) between patients with R/R AML receiving mitoxantrone, etoposide, and cytarabine alone or with lintuzumab.[12] Subsequently, a randomized phase II study failed to demonstrate survival benefit by adding lintuzumab to low-dose cytarabine in older untreated AML patients.[13] Based on these results, further clinical development was halted.

Mutagenesis strategies, computational design algorithms, and high-throughput screening methods have been used to optimize Fcγ receptor binding to increase the immunologic activity of mAbs. BI 836858 is a fully humanized Fc-engineered anti-CD33 mAb with enhanced binding affinity to Fcγ receptor IIIa on natural killer (NK) cells.[14] Decitabine was shown to increase ligands for activating NK receptors, thereby potentiating BI 836858 activity.[15] Based on these data, a phase I/II trial of BI 836858 and decitabine is now under way (NCT02632721). Talacotuzumab (CSL362; JNJ-56022473), a fully humanized Fc-engineered anti-CD123 mAb, was studied in patients with poor-risk AML in first or second complete remission (CR). Ten of 20 patients remained in CR for a median duration of over 34 weeks, and three of six MRD^+ patients became negative.[16] A randomized phase II/III trial of decitabine with or without talacotuzumab in patients with untreated AML who are not candidates for intensive chemotherapy is currently in progress (NCT02472145). Additionally, several anti-CD47 mAbs, including Hu5F9-G4 (NCT02678338), TTI-621 (NCT02663518), and CC-90002 (NCT02641002), have begun clinical development in AML and high-risk myelodysplastic syndrome (MDS).[17]

Bispecific Antibodies

Bispecific antibodies combine the specificities and biologic functions of two antibodies by targeting tumor-associated antigens and effector cells. These constructs bring effector cells into close proximity to tumor and activate their cytotoxic functions. Since the approval of blinatumomab, a bispecific T-cell engager (BiTE) against CD19 and CD3,[18] investigators have engineered various combinations of intact antibodies and fragments to produce more than 60 different bispecific formats.[19] Some of the more common are depicted in Figure 1. BiTEs and dual-affinity retargeting molecules (DARTs), which lack an Fc domain, can easily penetrate tumors because of their small size but have a short half-life, often necessitating delivery by continuous infusion. To address this issue, second-generation DARTs that bear an Fc domain and heterodimeric IgG-like bispecifics have been developed.

In preclinical studies, AMG 330, a BiTE targeting CD33 and CD3, was shown to activate and expand T cells from autologous samples of AML patients and mediate lysis of primary AML cells.[20] A phase I trial was initiated in patients with R/R AML but is currently on hold for safety concerns (NCT02520427). Similarly, JNJ-63709178, a humanized IgG4 bispecific antibody that binds CD123 and CD3, showed activity *in vitro* and in xenograft models,[21] but a phase I clinical study in R/R AML was placed on hold for serious side effects (NCT02715011). MGD006 is a DART made up of two independent chains targeting CD123 and CD3 attached in tandem. Promising preclinical data have led to an ongoing first-in-human study in patients with R/R AML and MDS (NCT02152956).[22]

Antibody-Drug Conjugates

Gemtuzumab ozogamicin (GO) consists of an anti-CD33 mAb conjugated to calicheamicin, a potent antitumor antibiotic. GO was approved in 2000 for the treatment of older patients with relapsed AML.[23] A randomized trial comparing daunorubicin and cytarabine induction with or without GO was stopped after an interim analysis showed increased peri-induction mortality in the GO arm.[24] No