Monoclonal Antibodies

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KEYWORDS

• Cutaneous lymphoma • Antibody therapy • Antibody conjugates • Clinical trials

KEY POINTS

- Monoclonal antibodies (mAbs) have been proved to be successful in hematologic malignancies, including cutaneous lymphomas.
- Some mAbs demonstrated high response rates (RRs) and a favorable toxicity profile in clinical trials.
- Safe and effective mAbs can be used as combinational agents and for sequential therapies in a rational stepwise therapy for cutaneous lymphomas.

INTRODUCTION

Since the initial description of the production of mAbs using hybridoma technology by Köhler and Milstein in 1975,[1] significant advances have been made in the use of mAbs and their derivatives in clinical practice. The technology has enjoyed many advances. Antibody immunogenicity progressively decreased from mouse to chimeric humanized to fully human mAbs. Various structural modifications to improve led to improvement of specificity of the antibodies and their targeted and selective cytotoxicity. Targeting specific cellular targets has been successful in hematologic malignancies and solid tumors, demonstrating significantly improved patient survival. Cutaneous lymphomas have also been successfully targeted with specific mAbs for B-cell or T-cell lymphomas and through nonspecific broad antitumor activity.

mAbs and their derivatives can be grouped using various classifications. mAbs can be classified based on their respective targets or functions, such as direct tumor cell killers, checkpoint blockade inhibitors, tumor microenvironment modifiers, or immune primers,[2] among others (**Table 1**). Currently available mAbs also can be classified by their alteration in immunoglobulin scaffold and/or addition of a conjugate designed to enhance immune activation or trigger direct cell death. Agents conjugated to mAbs include immunotoxins (ITs), such as the diphtheria toxin (DT), radioisotopes (radioimmunoconjugates, such as yttrium 90), or cytotoxic drugs (antibody-drug conjugates [ADC] such as auristatins). Most approved mAbs in clinical practice are unconjugated antibodies that exert antitumor effects through complement- or antibody-dependent cell-mediated cytotoxicity (ADCC).

Progress in biotechnology and improved understanding in cancer biology have sparked a flurry of inventions leading to improving effective mAb-based therapies while limiting overall drug toxicity.[3] Most of these antibodies are undergoing clinical investigation, and many show promise in clinical trials (see below). Engineering of new second- and third-generation mAbs and immunoconjugates with improved clinical efficacy and safety profile offers the potential of going further than optimization of naturally occurring antibodies. For example, defucosylation of the residues in the carbohydrate backbone of the antibody is thought to increase affinity for FcγRIIIa/b and other receptors, improving ADCC.[4] Certain modifications are capable of creating entirely new mAbs not found in nature, designed specifically to match desired characteristics, with nearly limitless possibilities.

The next generation of targeted biologics for cancer therapy in clinical development represents a wide variety of manmade rationally designed modifications of the antibodies directed toward

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Table 1
Classification of therapeutic antibodies based on their function

Action	Antibody Target
Tumor cell killing	CD2, CD3[a], CD4, CD25[a], CD30[a], CD52[a], CCR4[a], KIR3DL2
T-cell activation	PD-1[a], PD-L1[a], CTLA-4[a], CD137, OX40
Tumor microenvironment	CD25[a], PD-1[a], PD-L1[a], CD137, OX40, STAT3
Immune priming	CD40, CD137

Abbreviations: CTLA-4, cytotoxic T-lymphocyte antigen; KIR3DL2, killer cell immunoglobulin-like receptor 3DL2; PD-1, programmed death-1.
[a] In clinical practice.
Data from Martinez Forero I, Okada H, Topalian SL, et al. Workshop on immunotherapy combinations. Society for Immunotherapy of Cancer annual meeting Bethesda, November 3, 2011. J Transl Med 2012;10:108.

improved tissue penetration, efficacy, and safety. Antibody fragments,[5] dimers (diabodies),[6] bispecific and multispecific antibody derivatives,[7] and many other antibody alterations, including ADCs, possess novel characteristics, not normally observed in nature. Such novel molecules are capable of synergistically affecting many complementing pathways resulting in more effective blocking of malignant cell proliferation, angiogenesis, and tumor escape.[7] While this is an exciting area of investigation that will undoubtedly yield positive clinical results applicable to cutaneous lymphomas, it is beyond the scope of this discussion.

The US Food and Drug Administration (FDA) has now approved more than 20 mAbs for clinical use in various malignancies, and over 350 other mAbs are currently in the pipeline, including clinical trials in lymphomas. mAbs are now established as targeted therapies for malignancies, transplant rejection, autoimmune and infectious diseases, as well as a range of new indications. This article discusses FDA-approved mAb-based therapies for cutaneous lymphomas, mAbs used off-label for therapy for cutaneous lymphomas, and clinical trials of other mAbs that have the potential to be of benefit to patients with skin lymphomas.

ANTIBODIES CURRENTLY IN CLINICAL PRACTICE

Anti-CD52

The Campath series of mAbs was originally produced at the Cambridge University Pathology Department in the 1980s. Alemtuzumab (Campath) is a humanized IgG1 mAb directed against the CD52 antigen. CD52 is a nonmodulating glycoprotein expressed on lymphocytes, monocytes, and macrophages but not on stem cells or bone marrow progenitor cells. As CD52 is expressed by both B and T lymphocytes, alemtuzumab is immunosuppressive. This mAb causes lymphocyte lysis via ADCC and complement fixation and may also induce apoptosis. Alemtuzumab is approved by the FDA for patients with chronic lymphocytic leukemia (CLL) who have been treated with alkylating agents and have failed fludarabine therapy and for patients with relapsing multiple sclerosis. This mAb is used for CTCL off-label. Per package insert, alemtuzumab is administered as an infusion over 2 hours thrice a week in a dose-escalating manner starting at 3 mg, then increasing to 10 mg, and then up to 30 mg for a total of 12 weeks depending on tolerability. Because of marked immunosuppression due to the drug, careful monitoring for cytomegalovirus (CMV) reactivation and appropriate prophylaxis for PCP/herpes simplex virus/varicella zoster virus are recommended. Responses are generally evaluated at the end of the 12 weeks. However, alemtuzumab administration in CTCL differs from that recommended for CLL (see below).

In 2003, a phase 2 study conducted by Lundin and colleagues[8] reported on 22 patients with refractory, advanced, CD52-positive CTCL (7 patients with Sézary syndrome [SS] and 15 with advanced mycosis fungoides [MF]) successfully treated with alemtuzumab with an overall RR of 55% (32% complete response [CR], 23% partial response [PR]). The investigators reported better responses in erythrodermic patients with SS than in those with plaques or skin tumors and clearing of Sézary cells in 6 of 7 patients. After 10 years, this early observation was explained by Clark and colleagues[9] when they determined that in leukemic SS, alemtuzumab depleted recirculating benign and malignant central memory T cells in blood and skin of patients with SS, but did not affect a diverse population of sessile skin-resident effector memory T cells found in MF. Low-dose alemtuzumab (10 mg) was also associated with lack of infections in