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REVIEW

The development of potential antibody-based therapies for myeloma

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ABSTRACT

With optimal target antigen selection antibody-based therapeutics can be very effective agents for hematologic malignancies, but none have yet been approved for myeloma. Rituximab and brentuximab vedotin are examples of success for the naked antibody and antibody–drug conjugate classes, respectively. Plasma cell myeloma is an attractive disease for antibody-based targeting due to target cell accessibility and the complementary mechanism of action with approved therapies. Initial antibodies tested in myeloma were disappointing. However, recent results from targeting well-characterized antigens have been more encouraging. In particular, the CD38 and CD138 targeted therapies are showing single-agent activity in early phase clinical trials. Here we will review the development pipeline for naked antibodies and antibody–drug conjugates for myeloma. There is clear clinical need for new treatments, as myeloma inevitably becomes refractory to standard agents. The full impact is yet to be established, but we are optimistic that the first FDA-approved antibody therapeutic(s) for this disease will emerge in the near future.

1. Introduction

The FDA approval of the monoclonal antibody (mAb) rituximab in 1997 was the harbinger of a significant change to the treatment of cancer. This single agent has become a component of first and subsequent line therapy in many subtypes of non-Hodgkin lymphoma [1,2]. Central to efficacy of rituximab is the expression of its target antigen, CD20, on the cell surface. In solid tumors, the prototype for success is trastuzumab, a naked antibody that targets the human epidermal growth factor receptor 2 (HER2), which is approved for use in the treatment of breast cancer. Efforts to extend mAb therapy into other malignancies has been met with both resounding successes and costly failures, as only a small fraction of mAbs that have entered clinical trials in oncology have received FDA approval [3].

One potential way to improve upon the efficacy of mAbs is to use them as a targeted delivery system for chemotherapy. After years of research and development, antibody–drug conjugates (ADCs) have seen renewed excitement after the recent FDA approval for two new agents. The first is the anti-CD30 ADC brentuximab vedotin in Hodgkin lymphoma (HL) and anaplastic large cell lymphoma (ALCL). Early phase studies in patients with relapsed or refractory HL or ALCL have shown remarkable responses in the majority of patients, including significant numbers achieving complete response (CR), leading to accelerated FDA approval for these indications in 2011 [4,5]. Trastuzumab, targeting HER2, has also been utilized in this approach by linkage to another antitubulin cytotoxic (mertansine) to create ado-trastuzumab emtansine (T-DM1) [6]. T-DM1 is highly active in trastuzumab-resistant, HER2-positive breast cancer, leading to FDA approval in that setting [7]. Furthermore, T-DM1 was also found to be superior to trastuzumab in the first line setting, demonstrating the potential to improve upon the efficacy of naked antibodies [8]. Overall, the success of mAbs as novel cancer therapeutics has incited increasing efforts to broaden their application. Plasma cell myeloma (aka multiple myeloma) is one such disease where new therapy is needed, especially since this is an incurable disease and the development of resistance to current therapies is universal.

Abbreviations: ASCO, American Society of Clinical Oncology; ASH, American Society of Hematology; ALL, acute lymphoblastic leukemia; ALCL, anaplastic large cell lymphoma; ADCC, antibody-dependent cellular cytotoxicity; ADC, antibody–drug conjugate; BM, bone marrow; CAR-T, chimeric antigen receptor T-cell; CLL, chronic lymphocytic leukemia; CDC, complement-dependent cytotoxicity; CR, complete response; EC50, half maximal effective concentration; EBMT, European Group for Blood and Marrow Transplant; GO, gemtuzumab ozogamicin; FcrL5, Fc receptor-like 5; HLA, human leukocyte antigen; HER2, human epidermal growth factor receptor 2; HL, Hodgkin lymphoma; IMiDs, immunomodulatory drugs; IGF-IR, insulin-like growth factor 1 receptor; LAMP1, lysosomal-associated membrane protein 1; MHC, major histocompatibility complex; mAb, monoclonal antibody; MFI, median fluorescence intensity; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F; M-IC, myeloma initiating cells; ORR, overall response rate; MR, minor response; PR, partial response; PD-L1, PD1-ligand; PC, plasma cell; PD1, programmed death 1; SPEP, serum protein electrophoresis; SLAMF7, signaling lymphocyte activation molecule family member 7; SD, stable disease; T-DM1, ado-trastuzumab emtansine; TCR, T-cell receptor; TTP, time to progression; TNF, tumor necrosis factor; VGPR, very good partial response.

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2. Rationale for developing antibody-based therapy for myeloma

Efforts to broaden the applicability of naked antibodies to myeloma by targeting antigens more specific to the disease are finally coming to fruition, after several years of mostly disappointing clinical trials. Extrapolating from established agents in other malignancies, there are several mechanisms by which an antibody therapeutic could potentially destroy myeloma cells [1]. Most mAbs function by binding to an appropriate cell surface antigen, where the "naked" antibody can direct the patients' own immune system against the malignant cells, tagging them for elimination by antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) [9]. Many naked antibodies tested *in vitro* for myeloma have been shown to activate ADCC, but unfortunately this mechanism has demonstrated limited clinical activity by itself [2]. Inhibition of signal transduction is another mechanism that can contribute to the efficacy of clinically used antibodies. Thus, several antibodies were developed to target signaling pathways responsible for myeloma cell survival, proliferation and microenvironment interaction [3]. Efficacy can be accentuated by linkage of mAbs to cytotoxic small molecules (Fig. 1). These antibody–drug conjugates have the potential to be far more potent than their naked counterparts in tumor cell killing, when the target antigen is rapidly internalized. To date very few antibody–drug conjugates have been tested in myeloma. These "armed" antibodies may improve clinical efficacy and perhaps have the greatest promise for novel therapeutics in myeloma.

The treatment of myeloma has truly undergone a renaissance over the past 5–10 years. The use of proteasome inhibitors and IMiDs has drastically changed longevity for patients and the median overall survival now approaches a decade. Immunomodulatory drugs (IMiDs) have been thought to have pleiotropic immune effects. However, a critical mechanism of IMiD action was recently found to involve binding to Cereblon, a unique E3 ubiquitin ligase protein [10,11]. This interaction facilitates the degradation of Ikaros B-cell transcription factors [12]. The proteasome inhibitors also directly affect protein stability through inhibition of the chymotryptic site on the proteasome and producing a massive unfolded protein response [13]. The proteasome inhibitors and IMiDs have been used in combination with more traditional chemotherapy (alkylators and anthracyclines) and steroids to produce robust anti-myeloma effects in the frontline and relapse settings. However, despite these advances, resistance inevitably develops and the disease ultimately remains fatal. In addition, the disease can cause a debilitating course with a significant risk of skeletal disease (especially vertebral fractures), recurrent infections and/or kidney damage. Thus, there is still great need for novel therapeutics and new classes of drugs for this disease.

Antibody therapies provide exquisite targeting specificity and have the potential to greatly improve the outcome in this devastating disease. Malignant plasma cells (PCs) are primarily localized to the bone marrow (BM) and are readily accessible to intravenously infused antibody therapies through discontinuous capillaries (sinusoids) [14,15]. This contrasts to solid tumors, for which location and the capillary endothelium can present barriers to delivery [14,15]. The preclinical results for the many naked antibodies investigated for myeloma have been comprehensively reviewed previously [16]. Here, we will provide an update on a subset of the naked antibodies with emphasis on their clinical results, including CD38, signaling lymphocyte activation molecule family member 7 (SLAMF7/CS1), CD74, CD40 and insulin-like growth factor 1 receptor (IGF-IR/CD221). ADCs are now becoming the focus for this genre of drug development in myeloma. These will be emphasized here, with published targets consisting of CD138, CD56, Fc receptor-like 5 (FcRL5/CD307), CD74 and B-cell maturation antigen (BCMA).

3. Myeloma target antigens

One of the most important aspects of developing antibody-based therapeutic in myeloma is target antigen selection. Ideally the target should demonstrate selective overexpression on the malignant cells. HER2 is an analogous example, as the gene is amplified from 2 to greater

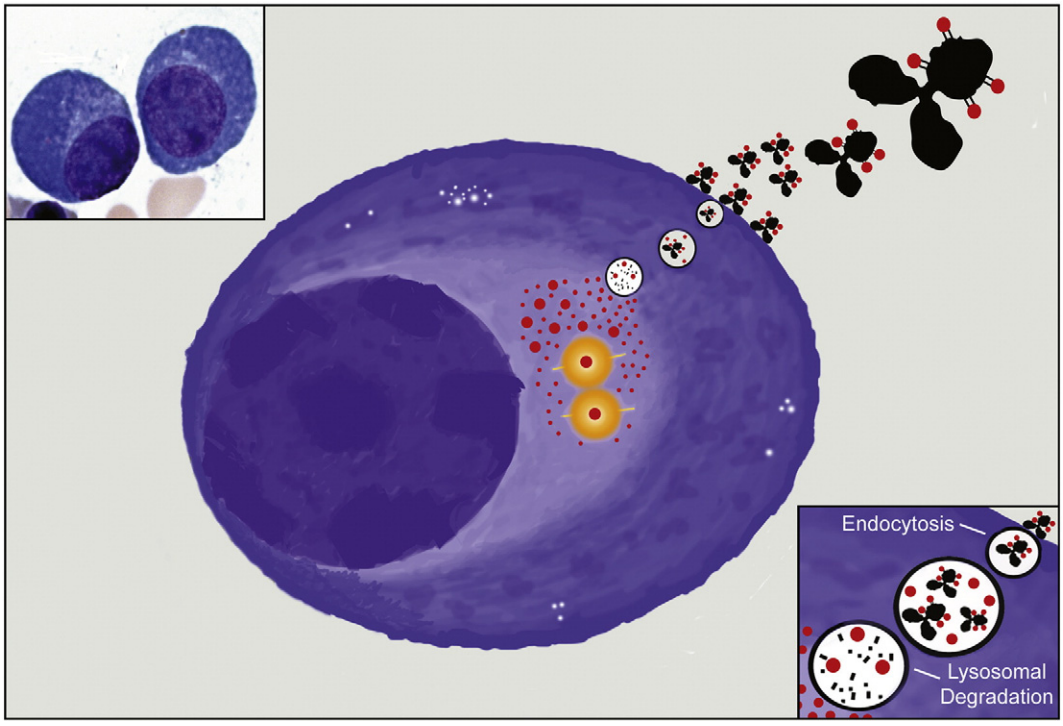

Fig. 1. Illustration of a malignant plasma cell showing the mechanism of action for antibody–drug conjugates. ADC targets are ideally selected for endocytosis and trafficking into lysosome (upper right corner, magnified in lower right corner), where the antibodies are broken down (black), leaving the cytotoxic payloads (red) to diffuse out into the cytosol. In the case of commonly employed auristatin and maytansine derivatives, the payloads bind at their sites of action and induce microtubule catastrophe (yellow/orange) and lead to cell death. Upper left myeloma cell micrograph courtesy Kristie White, UCSF Hematopathology.