How can we improve monoclonal antibody efficacy in myeloma ?

Niels van de Donk
Department of Hematology, VU Medical Center, Amsterdam, The Netherlands

In the last decade survival of multiple myeloma (MM) patients has markedly improved. However, despite this progress, patients with disease refractory to both IMiDs and proteasome inhibitors have a median overall survival of only 9 months, highlighting the need for additional agents with novel mechanisms of action. Monoclonal antibodies (mAbs) are an important new class of agents with unique mechanisms of action. MAbs against target antigens expressed on MM cells can induce tumor cell killing via a variety of mechanisms including Fc-dependent effector mechanisms including complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP). Importantly, they may also have direct effects via modulation of the activity of the targeted antigen.

Recently, the CD38-targeting antibody daratumumab (single agent) and the SLAMF7-targeting antibody elotuzumab (in combination with lenalidomide-dexamethasone) were approved by the FDA and EMA for the treatment of relapsed/refractory MM. Other CD38-targeting antibodies in advanced stages of development are isatuximab and MOR202.

mAbs are attractive partners in combination regimens, since mAbs have a favourable toxicity profile and distinct mechanisms of action, when compared to established anti-MM agents.

Preclinical evidence shows that lenalidomide enhances anti-MM activity of elotuzumab and CD38-targeting mAbs via activating the effector cells of ADCC, which formed the rationale for the clinical evaluation of these combinations. Indeed, a recently published phase 3 study showed impressive results of the combination of daratumumab with lenalidomide-dexamethasone as compared to lenalidomide-dexamethasone alone. Furthermore, although elotuzumab has no single agent activity, the combination of elotuzumab and lenalidomide-dexamethasone was superior to lenalidomide-dexamethasone alone. Also pomalidomide can be effectively combined with antibodies in MM.

Preclinical studies showing that the efficacy of elotuzumab and CD38-targeting antibodies was enhanced by bortezomib, formed the rationale for the clinical evaluation of the combination of bortezomib and a therapeutic antibody. Indeed clinical studies show that these combinations are well tolerated and active in relapsed/refractory MM.

In conclusion, the recent development of elotuzumab and selected CD38-targeting antibodies has proven transformative in MM. These mAbs are generally well tolerated and have marked activity either as a single agent and/or in combination with other anti-MM agents in relapsed/refractory MM. Clinical studies in the newly-diagnosed setting are ongoing.