Blood Reviews 30 (2016) 101–110

Contents lists available at ScienceDirect

Blood Reviews

journal homepage: www.elsevier.com/locate/blre

REVIEW

Monoclonal antibodies — A new era in the treatment of multiple myeloma

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ARTICLE INFO

Keywords:
Monoclonal antibodies
Multiple myeloma
Bone disease
Daratumumab
Elotuzumab
Siltuximab
Lorvotuzumab
Pembrolizumab
Denosumab
BHQ880

ABSTRACT

Monoclonal antibodies (mAbs) are currently the most investigated therapeutic compounds in oncology, but there is no monoclonal antibody approved in the treatment of multiple myeloma (MM). Nevertheless several really promising molecules are under investigation in phase III clinical trials. Dominantly daratumumab (anti-CD38) and elotuzumab (anti-CS1) showed extraordinary effectiveness in phase I/II trials. The toxicity was acceptable which is important for their addition to standard anti-myeloma agents like proteasome inhibitors or immunomodulatory drugs. Monoclonal antibodies such as denosumab (anti-RANKL) or BHQ880 (anti-DKK-1) are investigated also in the management of myeloma bone disease. This review is focused on the most promising mAbs, their mechanisms of action and the rationale of use. Practically all available results have been described. If the ongoing trials confirm the efficacy and safety of mAbs, they would become an important part of MM treatment that would be translated in the further improvement of therapeutic outcomes.

1. Introduction

Multiple myeloma ranks together with diffuse large B-cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL) amongst three of the most common hematological malignancies. This plasma cell disorder represents approximately 1% of all malignant tumors and its incidence is estimated to be 6 cases per 100,000 persons per year [1,2]. The introduction of autologous stem cell transplantation (ASCT) as well as novel agents such as immunomodulatory drugs (thalidomide and lenalidomide) and proteasome inhibitors (bortezomib), has dramatically improved treatment outcomes of myeloma patients. At present, median overall survival (OS) of patients eligible for ASCT is 6–8 years with one third of these patients living more than 10 years [3,4]. In elderly patients ineligible for ASCT the median OS is 4–6 years [5]. However, despite clear treatment advances, virtually all myeloma patients will eventually relapse. Patients who relapse after bortezomib and either thalidomide or lenalidomide, the so called "double refractory" patients, have a median OS of only 9 months [6]. This clearly demonstrates that there is a need for new treatment approaches that would be able to overcome a dismal course of the disease in these patients. A plethora of novel mechanisms and agents have been investigated recently. New generations of proteasome inhibitors (carfilzomib, ixazomib, oprozomib) and third generation of immunomodulatory drugs (pomalidomide) have been tested in many clinical trials, whereas carfilzomib and pomalidomide have already been approved for clinical use in several countries. Agents with novel mechanisms of action such as deacetylase inhibitors, mTOR/Akt inhibitors, kinesin spindle protein inhibitors (Arry-520), monoclonal antibodies and many others have been investigated in depth [7,8]. Monoclonal antibodies represent the most promising group of agents with unique mechanism of action in the treatment of multiple myeloma itself as well as in the treatment of bone disease accompanying approximately 80% of myeloma patients, being the most common complication in MM.

Bone disease and the skeletal complications associated with bone pain, pathological fractures requiring surgery and/or radiation, hypercalcemia and spinal cord compression can be devastating and seriously affect the quality of life and survival rate [9]. The main underlying cause of bone disease in MM is the predominance of bone resorption over bone production, respectively the superiority of osteoclasts over osteoblasts, resulting in the development of lytic lesions and/or osteoporosis [10]. At present, bisphosphonates remain the cornerstone in the treatment of multiple myeloma bone disease, nevertheless the better understanding of the biology of bone disease has led to the development of many novel agents. Several of them are monoclonal antibodies targeting certain molecules such as RANKL, Dickkopf-1 or sclerostin that play a crucial role in the pathogenesis of bone disease.

This review is focused on the current knowledge of monoclonal antibodies in the treatment of multiple myeloma and in the management of myeloma bone disease. All available results of clinical trials investigating mAbs are summarized in Tables 1 and 2.

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http://dx.doi.org/10.1016/j.blre.2015.08.004
0268-960X/

Table 1
Results of clinical trials conducted in RRMM patients.

Study	Phase	n	Median # of prior lines of therapy	ORR (%)	CR (%)
Monotherapy					
Thalidomide [77]	II	84	2	25	2.3
Bortezomib [78]	II	333	2	38	6
Carfilzomib [79]	II	257	5	23.7	0.4
Lenalidomide [80]	II	102	4	17	4
Pomalidomide [81]	II	221	5	18	2
Two-drugs regimen					
Len/Dex [82]	III	177	2	61	14.1
Pom/Dex [83]	III	302	5	31	1
Three-drugs regimen					
Len/Dex/Btz [84]	II	64	2	64	25
Len/Dex/Cfz [85]	II	52	3	76.9	5.7
Len/Dex/Ben [86]	I/II	29	3	52	0
Monoclonal antibodies					
Daratumumab [23]	I/II	32	6	42	0
Daratumumab [26]	II	106	5	29	3
Dara/Len/Dex [27]	I/II	20	4	75	15
Elotuzumab [31]	I	35	4.5	0	0
Elo/Btz/Dex [32]	I	28	2	47	7
Elo/Btz/Dex [33]	II	152	1–3	66	NA
Elo/Len/Dex [34]	I	29	3	82	4
Elo/Len/Dex [35]	Ib/II	101	2	84	14
Elo/Len/Dex [37]	III	646	2	79	NA
Siltuximab [45]	II	55	4	0	0
Sil/Btz [47]	II	142	2	55	11
Sil/Btz/Mel/Prednisone [46]	II	52	0	88	28
Lorvotuzumab [55]	I	37	6	5	0
Lor/Len/Dex [56]	I	44	2	56	2

NA — not applicable.

2. Monoclonal antibodies in the treatment of multiple myeloma

2.1. Daratumumab (HuMax™-CD38)

Many anti-CD38 monoclonal antibodies have been investigated in the past. Several of them such as SAR650984 (Sanofi), MOR03087 (Morphosys) or Ab79 (Takeda) are currently in the early phases of clinical testing, but daratumumab (Genmab/Janssen) seems to be the most promising. Daratumumab is a human IgG1κ monoclonal antibody targeted against CD38, that is a 46 kDa transmembrane glycoprotein [11]. This molecule is an ectoenzyme (cyclic ADP ribosylhydrolase) regulating the intracytoplasmic concentration of calcium, but it also behaves as a receptor, modulating interactions between cells and co-operating in transmembrane signal transmission [12]. Under normal conditions, CD38 is expressed at relatively low levels on the cell surface of myeloid and lymphoid cells as well as on some other tissues (neurons, epithelia, striated muscle) [13]. Myeloid cells are represented dominantly by neutrophils, eosinophils and basophils as well as CD14++ CD16− monocytes [14], lymphoid cells by most natural killer (NK) cells, mature T lymphocytes, B lymphocytes and plasma cells, respectively [15], (Fig. 1). Pluripotent hematopoietic precursor cells (HPC) that are crucial for long-term marrow recovery do not express CD38 at all. Overexpression of CD38 is seen in a majority of lymphoid tumors, but on malignant plasma cells in multiple myeloma this antigen is highly expressed (CD38++) in comparison to other cell types [16] making it an attractive target for antibody therapy.

Daratumumab, as well as other monoclonal antibodies, possess a broad spectrum of killing activities. ADCC (antibody-dependent cell-mediated cytotoxicity) is the killing of an antibody-coated target cell by a cytotoxic effector cell through a nonphagocytic process,