Critical Reviews in Oncology / Hematology 121 (2018) 74–89

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

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

A question of class: Treatment options for patients with relapsed and/or refractory multiple myeloma

Gordon Cook[a,*], Sonja Zweegman[b], María-Victoria Mateos[c], Florence Suzan[d], Philippe Moreau[e]

[a] St James's Institute of Oncology, Leeds Teaching Hospitals NHS Trust and University of Leeds, Leeds, UK
[b] Department of Hematology, VU University Medical Center, Amsterdam, Netherlands
[c] Hematology Service, University Hospital of Salamanca/IBSAL, Salamanca, Spain
[d] Amgen (Europe) GmbH, Zug, Switzerland
[e] Department of Hematology, University of Nantes Health Centre, France

ARTICLE INFO

Keywords:
Multiple myeloma
Relapsed
Refractory
Elderly
Cytogenetics

ABSTRACT

Multiple classes of agent with distinct mechanisms of action are now available for the treatment of patients with relapsed and/or refractory multiple myeloma (RRMM), including immunomodulatory agents, proteasome inhibitors, histone deacetylase inhibitors and monoclonal antibodies. Additionally, several different drugs may be available within each agent class, each with their own specific efficacy and safety profile. This expansion of the treatment landscape has dramatically improved outcomes for patients. However, as the treatment options for RRMM become more complex, choosing the class of agent or combination of agents to use in the relapsed setting becomes increasingly challenging. Furthermore, treatment options for specific patient populations such as the elderly, those with high-risk cytogenetic abnormalities and those with refractory disease are yet to be defined in the current treatment landscape. When choosing an appropriate treatment approach, physicians must consider multiple criteria including both patient-related and disease-related factors. The aim should be to provide patient-specific treatment in order to gain a clinical benefit while minimizing toxicity. This review provides an overview of the mechanism of action and efficacy and safety profiles of each class of agent and of treatment regimens that combine different classes of agent, with a special focus on treating specific patient populations.

1. Introduction

Multiple myeloma (MM) is characterized by a relapsing disease course. Despite significant improvements in patient outcomes following the introduction of immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs) in the first-line setting (Kumar et al., 2008), most patients eventually relapse, and the management of relapsed and/or refractory MM (RRMM) remains a challenge (Laubach et al., 2016). The treatment landscape for patients with RRMM is rapidly changing following the recent approval of three drugs belonging to two novel classes of agent in this setting: a histone deacetylase (HDAC) inhibitor (HDI), panobinostat (Farydak, 2016a; Farydak, 2016b), and two monoclonal antibodies (mAbs), daratumumab and elotuzumab (Squibb, 2015; Squibb, 2016; Darzalex, 2015; Darzalex, 2016). Furthermore, the addition of the second-generation IMiDs lenalidomide and pomalidomide (Celgene Corporation POMALYST, 2016; Celgene Europe Ltd., 2016a; Celgene Corporation Revlimid, 2013; Celgene Europe Ltd., 2016b) and the second-generation PIs carfilzomib and ixazomib (Kyprolis, 2015; Kyprolis, 2016; Millennium Pharmaceuticals Ninlaro, 2015; Takeda Pharma Nilaro, 2016) provides additional within-class treatment options for patients with RRMM. With multiple classes of agent now available, each with differing mechanisms of action and efficacy and safety profiles, it can be difficult for physicians to decide upon the most appropriate agent to use. In the relapsed setting, treatment choice is additionally influenced by a number of patient- and disease-related factors such as age, cytogenetics, pre-existing toxicities, aggressiveness of relapse, previous therapy, response to previous therapy and number of previous therapy lines (Laubach et al., 2016; Cornell and Kassim, 2016; Moreau et al., 2013). Patients should not be defined by one single characteristic: multiple factors should be considered in order to tailor treatment to the individual needs of each patient. Here we provide an overview of the different classes of agent currently approved for the treatment of RRMM and the factors that should guide treatment decisions. We also discuss additional considerations for treating elderly patients, those with high-risk cytogenetic abnormalities and those with refractory disease.

* Corresponding author.
E-mail address: g.cook@leeds.ac.uk (G. Cook).

https://doi.org/10.1016/j.critrevonc.2017.11.016
Received 25 April 2017; Received in revised form 14 November 2017; Accepted 30 November 2017

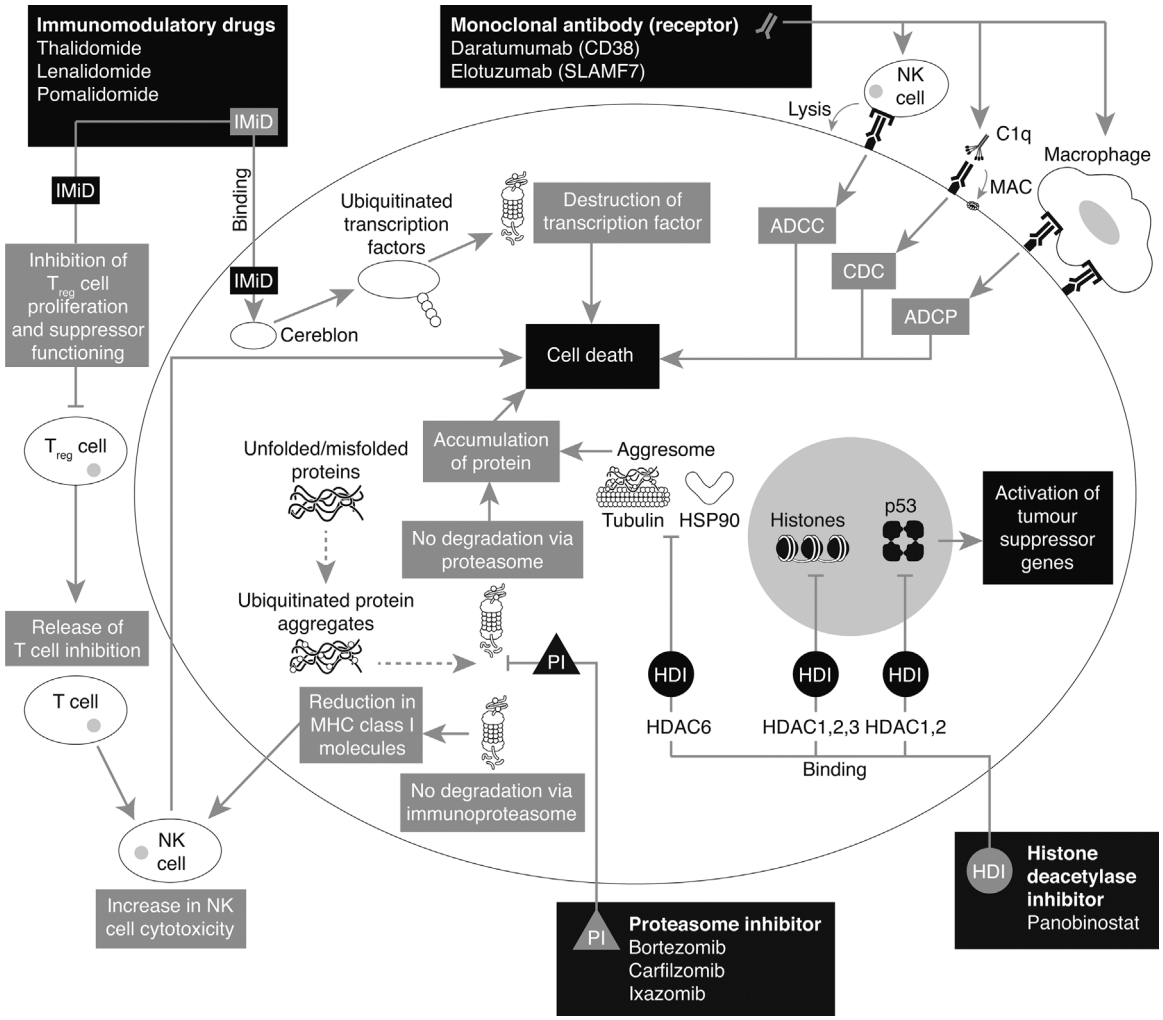

Fig.1. Summary of sub-cellaulr pathway-directed novel agents.

2. Classes of approved agent

2.1. Immunomodulatory drugs

The IMiD thalidomide, a synthetic derivative of glutamic acid, was the first immunomodulatory agent to be used for the treatment of MM (Celgene Corporation Thalomid, 2014; Celgene Europe Ltd., 2016c; Quach et al., 2010). The second-generation IMiDs lenalidomide and pomalidomide are thalidomide analogues (Quach et al., 2010). IMiDs possess multiple anti-myeloma properties that include immune modulation, along with anti-angiogenic, anti-inflammatory and anti-proliferative effects, which are mediated through direct and indirect mechanisms (Quach et al., 2010; Zhu et al., 2013). A direct anti-myeloma mechanism of IMiDs was recently determined with the identification of the IMiD target cereblon, an adaptor subunit of the E3 ubiquitin ligase that is required for their anti-myeloma activity. The binding of an IMiD to cereblon alters its substrate specificity, resulting in aberrant proteasomal degradation of the transcription factors Ikaros and Aiolos; this leads to downregulation of the pro-myeloma interferon regulatory factor 4 (Fig. 1). Lenalidomide, but not thalidomide or pomalidomide, has also been shown to cause cereblon-mediated degradation of casein kinase 1α, which leads to p53 activation (Ito and Handa, 2016). Indirect mechanisms of IMiDs include immunomodulation mediated through enhancement of CD4+ and CD8+ T cell co-stimulation, downregulation of inflammatory cytokines and augmentation of anti-myeloma natural killer cell activity (Zhu et al., 2013). Lenalidomide and pomalidomide additionally inhibit regulatory T cells (Zhu et al., 2013). Lenalidomide and pomalidomide are approved in the USA and Europe for the treatment of patients with RRMM (Table 1).

2.2. Proteasome inhibitors

The PIs bortezomib, carfilzomib and ixazomib target the ubiquitin–proteasome system, which is responsible for the degradation of intracellular proteins and the maintenance of cellular protein homeostasis. Inhibition of this system affects a number of components in cell-signalling pathways, leading to cell-cycle arrest, promotion of apoptosis and disruption of the stress response (Shah and Orlowski, 2009) (Fig. 1). MM cells are particularly sensitive to proteasome inhibition because they produce large quantities of protein in the form of immunoglobulin chains, and are dependent on proteasome-controlled signalling pathways for protein degradation (inhibition of which leads to the toxic accumulation of aggregated proteins) (Shah and Orlowski, 2009). Targeting the immunoproteasome, the proteolytic activity of which generates peptide substrates optimized for presentation on the major histocompatibility complex (MHC) class I molecules, is also relevant in MM because expression of the immunoproteasome is elevated in cells of haematopoietic origin (Kuhn and Orlowski, 2012). Inhibition of the immunoproteasome reduces surface expression of host protein fragments on MHC class I molecules, and thus may enhance natural killer cell-mediated cytotoxicity (Altun et al., 2005). Data suggest that the inhibition of both the constitutive proteasome and the immunoproteasome may be required for MM cell cytotoxicity (Kuhn and Orlowski, 2012).