



Evolving Therapy in Relapsed Myeloma

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Submission: December 16, 2016; **Published:** December 21, 2016

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Abstract

In the absence of a true cure, malignant plasma cell clones become increasingly aggressive and increasingly refractory to frontline treatments over time, prompting relapse, progression and death [1]. Patients who are refractory to newer agents such as lenalidomide and bortezomib have historically had a poor prognosis with a median event free survival of 5 months and median OS of 9 months [2]. The availability of several novel classes of drugs has provided a challenge for choice of therapy and allowed achievement of deep responses even in the relapsed setting [2].

Abbreviations: MM: Multiple Myeloma; PN: Peripheral Neuropathy; OS: Overall Survival; TTP: Time To Progression; XPO1: Exportin 1; TOP2: Topoisomerase II; CR: Complete Response; VGPR: Very Good Partial Response; PR: Partial Response; R/RMM: Relapsed/Refractory Multiple Myeloma; MRD: Minimal Residual Disease; PIs: Proteasome Inhibitors; IMiDs: Immunomodulatory Drugs; ORR: Overall Response Rates; PFS: Progression-Free Survival; PD1: Programmed Cell Death 1

Introduction

Although bortezomib- and lenalidomide-based regimens have proven effective in relapsed disease, repeatedly relapsed or high-risk clones can become refractory to one or both of these agents [1]. Pomalidomide, carfilzomib and ixazomib remain “second line” for relapsed patients who have developed refractoriness to lenalidomide and bortezomib [2]. The depth of response can affect long-term outcome in relapsed MM [3]. In the APEX trial the achievement of CR with bortezomib was associated with a longer time to next treatment compared with VGPR or PR (24 vs. 13 vs. 6 months) [4]. In the MM-009 and MM-010 trials, TTP and OS were significantly longer with achievement of VGPR or better using lenalidomide plus dexamethasone compared with PR (TTP: 27 vs. 12 months; OS: not reached vs. 44 months) [5]. At subsequent relapses and in R/RMM virtually no impact of CR/VGPR on OS or TTP is observed with pomalidomide plus low-dose dexamethasone as demonstrated in the MM-003 trial [6].

CR may be a relevant treatment goal which can be actively pursued in patients in first relapse. Clinically relevant responses can be achieved in 40 - 50% of patients in first relapse [3]. However, in patients with R/RMM, minimal response may be a clinically relevant outcome of treatment [6]. In second relapse and beyond the goal of treatment is to prevent organ impairment and to control the disease [3].

Triplet at First Relapse

The choice of treatment at relapse is determined by the type, response, and duration of initial therapy as well as disease factors, patient factors, and patient preference. Those who relapse

following a short duration of remission after upfront therapy, including autologous stem cell transplant, or symptomatic relapse with significant clinical symptoms or disease relapse in high-risk cytogenetics are generally considered to be aggressive relapses [7]. The ideal sequence of therapies is not known, although the field is moving toward combination triplet therapy at first relapse in fit patients [7].

For retreatment with an agent used previously, the minimal depth of the initial response should be PR and the minimal duration should be at least 6 months with acceptable treatment toxicity [3]. Multiple heterogeneous clonal populations evolve with treatment. Varying clones may alternate dominance over time what is known as “clonal tiding” [2]. Given the evidence for clonal tides, switching drug classes is likely beneficial, especially in higher-risk disease [7].

Carfilzomib: a novel second-generation PI, which gained approval in combination with lenalidomide and dexamethasone for treatment of relapsed MM patients who have received one to three prior lines of therapy [1]. Carfilzomib/IMiD triplet should be considered in aggressive relapses, given the excellent data of rapid induction of response and high rates of MRD negativity [7]. It offered a therapeutic benefit to patients who relapsed from bortezomib treatment with lower incidence of polyneuropathy. Nonetheless, drug resistance was also observed following carfilzomib treatment which is a known P-gp substrate [8].

Ixazomib: an oral boronic acid-based PI approved by US FDA in November 2015 in combination with lenalidomide and dexamethasone for treatment of MM patients who have received

at least one prior therapy. Preclinical results demonstrated that ixazomib inhibits the chymotrypsin-like proteolytic ($\beta 5$) site of the 20S proteasome, reduces tumor progression by increasing MM cell apoptosis, and disrupts the interaction of MM cells with the BM microenvironment resulting in decreased angiogenesis and osteolytic lesions [9]. The addition of ixazomib is a consideration in relapsed patients after an extended period of maintenance lenalidomide (eg, over a year) or in a biochemical relapse only [2]. An ixazomib-based regimen is also an option if an oral regimen is desired, especially in del (17p) or extramedullary disease [7]. Side effects are manageable and infrequent, including rash, lowered platelet and white blood cell counts, fatigue, diarrhea, and nausea, with a few instances of PN [9].

Elotuzumab: targets CD319 surface antigen, the protein encoded by the SLAMF7 gene. It was FDA approved on November 30, 2015 in combination with lenalidomide and dexamethasone for treatment of MM patients having had one to three prior lines of treatment [10]. Elotuzumab-based treatment could be considered in individuals who are frail or have underlying cytopenias [7]. Elotuzumab activity against disease with high risk cytogenetic features such as t (4; 14) and del (17p) has been reported. Its common adverse events are neutropenia (grade 3/4) and lymphocytopenia (grade 3/4) [11].

Daratumumab: a human immunoglobulin G1 kappa monoclonal antibody that binds malignant cells expressing CD38 with high affinity and induces tumor cell death through complement-dependent cytotoxicity, antibody-dependent cellular phagocytosis, antibody-dependent cell-mediated cytotoxicity, induction of apoptosis, and modulation of CD38 enzyme activities. In addition, daratumumab may also have an immunomodulatory role via T-cell activation and expansion as well as mitigation of immune suppression in MM patients [12]. Daratumumab in combination with either lenalidomide or bortezomib and dexamethasone was approved by the U.S. FDA on November 21, 2016 for the treatment of patients with MM who has received at least one prior therapy [13].

Relapse After ≥ 2 Lines of Therapy

The median OS of R/RMM patients who were double refractory to a PI and an IMiD or had relapsed after ≥ 3 prior lines of therapy, including the novel agent spomalidomide and carfilzomib was 8 months [12]. The median OS was found to be longer in patients younger than 65 years than for those who were at least 65 years. The same was true among patients with good performance status compared to those with poor performance status [14]. Duration of response is known to decrease with successive rounds of treatment [8]. Thus, new, effective therapies are needed for the management of patients who have exhausted treatment with bortezomib, lenalidomide and thalidomide [6].

Daratumumab monotherapy: approved by the FDA in 2015 to treat MM patients who had received at least 3 prior

therapies including either a PI or an IMiD, or those who are double-refractory to a PI and an IMiD [12]. An open label, multicenter study investigated daratumumab in combination with pomalidomide and dexamethasone in R/RMM patients with at least two lines of prior therapy. The ORR was 58.5%, including a 57.5% response rate in patients who were double-refractory to a PI and an IMiD. The six-month estimated PFS was 66%. The most common hematological side effects of any grade ($\geq 20\%$) were anemia, thrombocytopenia, and neutropenia [11]. At ASH 2016, data from the PAVO trial show that subcutaneous administration of daratumumab with recombinant human hyaluronidase enzyme (rHuPH20) has preliminary efficacy and adverse effects similar to IV daratumumab [15].

Pomalidomide: a third-generation IMiD that was approved by the FDA in February 2013, for use alone or in combination with dexamethasone, in R/R MM patients who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression within 60 days of their most recent treatment [1]. A pomalidomide-based regimen could be considered in aggressive relapse (eg with extramedullary disease or skeletal-related events) or in early relapse (eg < 1 year of lenalidomide maintenance following initial therapy with RVD) [7] and with del (17p) [7]. It has demonstrated a relatively tolerable safety profile with the most common grade 3/4 toxicities being hematologic (neutropenia, anemia and pancytopenia), infectious events with lower rate of venous thrombo embolism. Concurrent use of VTE prophylaxis has been recommended [1].

Panobinostat: a histone deacetylase inhibitor. This group increases the acetylation of histones, thus modulate the transcriptional profile of cells and affects nuclear events. HDAC inhibitors have various effects such as protein degradation through its effect on non-histone substrates [2]. Panobinostat is approved by the FDA in February 2015, in combination with bortezomib and dexamethasone, for treatment of MM patients who have received at least two prior standard therapies (including bortezomib and an IMiD) [1]. It has a limited role in first relapse because of the toxicity profile unless it is used to restore PI sensitivity in those relapsing after prior PI regimens [7].

Future Therapy

With over 12,000 deaths from MM anticipated in 2016, nearly all patients with MM will become “quad refractory” to IMiDs (lenalidomide and pomalidomide) and PI (bortezomib and carfilzomib) and eventually “penta refractory” to anti-CD38 Abs [16]. It is in the arena of such relapsed and refractory disease that novel agents enter into investigational use [1]. The most promising investigational new agents in MM include **isatuximab**, an anti-CD-38 monoclonal antibody; next generation PIs **oprozomib** (which is given oral) and **marizomib**, **filanesib** (ARRY-520), a kinesin spindle protein inhibitor; **dinaciclib**, a cyclin-dependent kinase inhibitor; **venetoclax** (ABT-199), a

selective BCL-2 inhibitor; and LGH-447, pan PIM kinase inhibitor [17]. **Chimeric antigen receptor T-cell therapy** has arrived for MM and may potentially change the paradigm of therapy [2].

Oprozomib: Twenty-nine patients with R/R MM were enrolled in a dose escalation study of oprozomib/dexamethasone combination therapy. The primary challenge to tolerability was gastrointestinal with frequent diarrhea, nausea and vomiting. However, none of the enrolled patients demonstrated new or worsening of baseline neuropathy. Preliminary response rates in phase 1 studies of heavily pretreated patients have been encouraging though sample sizes remain small [1].

Isatuximab (SAR650984): is a CD38 monoclonal antibody. It may act through antibody-dependent cellular cytotoxicity; complement-dependent cytotoxicity; antibody dependent cellular phagocytosis; direct apoptosis; and inhibition of myeloid-derived suppressor cells resulting in the release of T-cell suppression. It has shown significant clinical activity in heavily pretreated patients with at least five lines of therapy, including pomalidomide, lenalidomide and/or carfilzomib. Its most common adverse events have been fatigue, nausea, cough, dyspnea, anemia, thrombocytopenia and neutropenia. Infusion associated reactions occur in ~ 50% of patients and are limited mainly to cycle 1 [17]. Other target of monoclonal antibody therapy include **B-cell maturation antigen** (BCMA). Bispecific T cell engager antibodies are being developed targeting BCMA [2].

Filanesib (ARRY-520): a kinesin spindle protein inhibitor that arrests cells undergoing mitosis and promotes apoptosis. In highly refractory MM patients, single agent filanesib resulted in a 16% PR and when combined with dexamethasone, the PR increased to 22%. Filanesib in combination with low dose dexamethasone has shown a manageable safety profile [11].

Venetoclax: can potentially have a major role in the treatment of MM. Its activity as a single agent in myeloma therapy is promising, especially in [11,14] myeloma. With its unique mechanism of action and evident ability to enhance the activity of drugs, it is beneficial for future use in new non-cross-resistant regimens for myeloma therapy. It is well tolerated and has exhibited minimal side effects [17].

Selinexor (XPO1 inhibitor): XPO1 inhibitors are able to prevent nuclear export and promote nuclear accumulation of the tumor suppressor protein p53, and prevent the export of the drug target TOP2A. XPO1 inhibitors will sensitize drug-resistant myeloma cells to the TOP2 inhibitor doxorubicin. The combination of an XPO1 inhibitor and liposomal doxorubicin was highly effective against acquired drug resistance in in vitro MM models, and in ex vivo samples of relapsed/refractory myeloma patients. This drug combination synergistically induced TOP2A-mediated DNA damage and subsequent apoptosis [18].

Vorinostat: A phase IIb trial of vorinostat, a class I/II histone deacetylase inhibitor in combination with lenalidomide and

dexamethasone was active in heavily pre-treated population, refractory to previous lenalidomide-containing regimens [19]. Selective inhibition of specific HDAC6 inhibitor which includes the selective HDAC inhibitor ACY-241 is under investigation. It may be better tolerated than pan HDAC inhibition [2].

Pembrolizumab: Interim results from phase 2 study of PD1 inhibitor, pembrolizumab in combination with pomalidomide and dexamethasone have resulted in an overall response rate of 60% in 27 patients with heavily pretreated R/R MM [20].

Nelfinavir (HIV protease inhibitor): the addition of nelfinavir to bortezomib restored the activity of bortezomib in two thirds of bortezomib refractory myeloma including patients with high-risk disease cytogenetics without adding significantly to toxicity seen in bortezomib heavily pretreated myeloma. Induction of the unfolded protein response by nelfinavir results in apoptosis and is a major mechanism of cytotoxicity of proteasome inhibitors in MM (clinicaltrials.gov identifier: 01164709) [21].

Conclusion

The choice of which novel agent to use is not yet subject to a rigid paradigm and is decided on a case by case basis, with thought given to the nature of the preceding line (s) of treatment, availability, cost, and tolerability [1].

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