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Proteasome inhibitor-based therapy for treatment of newly diagnosed multiple myeloma

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ABSTRACT

Multiple myeloma is a hematologic malignancy that is unable to be cured and has significant impact throughout the world. Front line treatment has shifted but ultimately has landed on a bortezomib-based combination therapy. Carfilzomib is a next-generation proteasome inhibitor shown to improve both progression-free and overall survival in relapsed and refractory multiple myeloma in combination with lenalidomide and dexamethasone (KRd). Given the favorable response rates seen in phase II trials treating newly diagnosed myeloma, this combination is listed as a viable option for upfront treatment. This systematic review compares pharmacologic properties, clinical efficacy, and toxicities of carfilzomib- and bortezomib-based regimens.

1. Introduction

Multiple myeloma is an incurable hematologic neoplasm that has notable worldwide impact [1,2]. The treatment landscape has evolved over time to include risk-adjusted therapy at diagnosis, consolidation with high-dose chemotherapy and autologous stem cell rescue, as well as maintenance therapy [3]. While the development of these treatment strategies has followed a typical course, the bulk of new US Food and Drug Administration (FDA) approvals for relapsed and refractory disease have taken place in the last 3 years [4].

The choice of induction regimen for patients with newly diagnosed multiple myeloma has also evolved in the last decade. Bortezomib (Velcade; Millennium Pharmaceuticals, Cambridge, MA) is a first-in-class proteasome inhibitor and was approved by the FDA for upfront treatment of multiple myeloma in 2008 [5]. This approval was based on the results of an international multicenter randomized clinical trial of oral melphalan and prednisone with and without bortezomib [6,7]. The addition of bortezomib improved time to progression, progression-free survival, and overall survival. More recently, a randomized clinical trial from the Southwest Oncology Group (SWOG0777 trial) demonstrated that the addition of bortezomib to lenalidomide and dexamethasone (RVd) resulted in significantly improved progression-free and overall survival [8]. Based on these and other trials, bortezomib-based combination therapy is the accepted standard of care as induction therapy for patients with newly diagnosed multiple myeloma [9].

Carfilzomib (Kyprolis, Onyx Pharmaceuticals, South San Francisco, CA) is a next-in-class proteasome inhibitor that was FDA approved on July 20, 2012 for use in patients with multiple myeloma who have received at least two prior therapies, including treatment with bortezomib and an immunomodulatory therapy (such as lenalidomide), and have demonstrated disease progression on or within 60 days of completion of the last therapy [10]. Subsequently, the results of the randomized ASPIRE study confirmed the efficacy of the combination of carfilzomib, lenalidomide, and dexamethasone (KRd) in patients with relapsed multiple myeloma [11]. Compared with lenalidomide and dexamethasone, KRd resulted in improved progress-free and overall survival, leading to FDA approval for this indication [11]. Carfilzomib is not currently approved by the FDA for patients with newly diagnosed multiple myeloma. However, several phase II trials have demonstrated high overall response rates (ORR) and deeper responses (including minimal residual disease negativity) when the combination of KRd is used as induction therapy for newly diagnosed multiple myeloma patients [12,13]. Based on these early promising results, the National Comprehensive Cancer Network (NCCN) has included KRd as a possible option for induction therapy in patients with multiple myeloma.

In this systematic review, the pharmacologic properties, clinical efficacy (response rate, progress-free and overall survival), and toxicity of carfilzomib- and bortezomib-based regimens in newly diagnosed multiple myeloma are compared.

2. Pharmacologic properties

Table 1 compares some of the pharmacologic characteristics of both bortezomib and carfilzomib [14,15]. Both of these drugs

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Table 1
Comparison of pharmacology for bortezomib and carfilzomib.

	Bortezomib	Carfilzomib
Mechanism of action	Modified dipeptyl boronic acid proteasome inhibitor that reversibly binds to N-terminal threonine-containing active site of the 20S proteasome subunit	Tetrapeptide epoxyketone proteasome inhibitor that irreversibly binds to N-terminal threonine-containing active site of the 20S proteasome subunit
Maximum serum concentration (C_{max})	112 ng/mL	4,232 ng/mL
Half-life	66 to 108 hours	≤1 hour
Steady-state volume of distribution	4.3L	28L
Recommended dosing	Administered as intravenous bolus injection on days 1, 4, 8, and 11 of a 21-day cycle at a dose of 1.3 mg/m^2 Bortezomib is now commonly used a subcutaneous injection with the same schedule	Administered on days 1, 2, 8, 9, 15, and 16 on a 28-day cycle at a dose of 20 mg/m^2 for cycle 1 and 27 mg/m^2 beginning cycle 2 In newly diagnosed myeloma, dose of 36 mg/m^2 has been used

inhibit the 20S proteasome, one (bortezomib) reversibly and one irreversibly (carfilzomib) binding to the N-terminal threonine-containing active site of the proteasome subunit.

Both drugs are administered similarly but have different dosing schedules. Bortezomib can be given intravenously or subcutaneously, typically on days 1, 4, 8, and 11 of a 21-day cycle at a dose of 1.3 mg/m^2. Carfilzomib is given intravenously only and on days 1, 2, 8, 9, 15, and 16 on a 28-day cycle at a dose of 20 mg/m^2 for cycle 1 and 27 mg/m^2 beginning cycle 2.

The maximum serum concentration of carfilzomib is more than 37 times greater than that of bortezomib. Both of these drugs have IV formulations but bortezomib also has subcutaneous administration.

3. Recommendations for triplet therapy

Table 2 lists and compares FDA approvals for the treatment of myeloma in the upfront and relapsed/refractory setting with the guidelines put forth by the NCCN.

3.1. Newly diagnosed multiple myeloma

The FDA gave an expanded indication for RVd in the upfront setting in 2015. NCCN gave RVd a category 1 recommendation in the upfront setting. KRd was given a category 2B rating for newly diagnosed multiple myeloma.

3.2. Relapsed/refractory

The FDA approvals for RVd in the treatment of myeloma include an expanded indication in the upfront setting in 2016 from a previous indication of RVd after at least 1 prior therapy in 2006. The NCCN generally recommends re-induction with initial therapy if the relapse appears at greater than 6 months. They also gave a category 1 rating to KRd in the relapsed setting.

4. Treatment outcomes

4.1. Response rate

RVd has been studied in four prospective clinical trials as induction therapy for newly diagnosed multiple myeloma patients (one randomized phase III trial and three phase II trials) [8,16–18]. The ORRs reported for upfront treatment with RVd were between 73% and 100%, and the complete response (CR) rates reported were between 7% and 29% (Table 3). The ORR reported in two phase II trials [12,13] valuating KRd in untreated myeloma were both 98%, and the CR rates [19] reported for KRd in these trials were 42% and 43% (Table 3).

4.2. Progression-free survival

Two of the four upfront RVd trials reported progression-free survival at 1 year and were 68% and 77%. The reported progression-free survival at 1 year for upfront KRd in the two listed trials were 97% and 95%.

4.3. Overall survival

The reported overall survival at 1 year for upfront RVd were both 100%. For the two reported upfront KRd trials, overall survival at 1 year was 97% and 100%.

In summary, both RVd and KRd induction have high and comparable ORR based on single-arm phase II trials, while KRd has higher rates of CR. At short follow-up, KRd has superior progression-free survival with similar overall survival compared with RVd.

5. Toxicity

The toxicity profiles of the two regimens (ie, KRd and RVd) are distinct and three key adverse events were focused on: peripheral neuropathy, cardiac adverse events, and thromboembolic events.

Table 2
Comparison of FDA and NCCN recommendations for use of RVd and KRd regimens in multiple myeloma.

	FDA	NCCN
Newly diagnosed MM	RVd - expanded indication for untreated patients (2015) KRd - not approved	RVd - category 1 recommendation KRd - category 2A recommendation
Relapsed/refractory MM	RVd - at least 1 prior therapy (2006) KRd - 1 to 3 lines of previous therapy (2015)	RVd - recommended KRd - category 1 recommendation

Abbreviations: FDA, US Food and Drug Administration; KRd, lenalidomide and dexamethasone; MM, multiple myeloma; NCCN, National Comprehensive Cancer Network; RVd, bortezomib, lenalidomide, and dexamethasone.