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Review article

Emerging therapies for multiple myeloma: Application in older adults

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ABSTRACT

Tremendous advances in the treatment of multiple myeloma have yielded improvements in survival in patients with multiple myeloma. A number of pivotal phase III trials have established the benefit of these newer agents in individuals with relapsed multiple myeloma. Because older adults are under-enrolled in clinical trials, clinical trial data may not be categorically generalizable to more vulnerable older adults. In this review, the applicability to older adults of recent clinical trials of newer agents in older adults with myeloma are examined, with attention to eligibility criteria, dosing of therapy, characteristics of the population, and subgroup analyses of older adults.

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1. Introduction

Multiple myeloma (MM) is the second most common hematologic malignancy. With the aging of the population, a 90% increase in the number of people in the United States aged 64–84 with MM is forecast over the next 15 years [1]. While MM remains incurable, advances in treatment and supportive care have resulted in improved survival over the past 20 years [2,3]. Multiple therapeutic agents with novel mechanisms of action have been introduced and received regulatory approval based upon the results of large Phase III trials. Unfortunately, clinical trials continue to under-enroll and, in some cases, overtly exclude older patients [4,5]. In a review of actively recruiting clinical trials listed in the National Institutes of Health Registry (clinicaltrials.gov) in 2013, 19% of MM trials explicitly excluded patients over the age of 75, and 63% disproportionately excluded older patients due to exclusions based on age, performance status or comorbidities [4]. This results in limited data on the benefits and risks of newer therapies on older adults. With the flood of newer agents examined in recent pivotal Phase III trials, coupled with the increasing number of older patients with MM, it is timely to examine how this evidence base applies to older adults with MM [1]. This review will examine the eligibility criteria, planned baseline dose adjustments by age or comorbidity, characteristics of patients involved in the trials and age-specific subgroup analyses to determine the applicability of the results to treating older patients with MM.

1.1. Second Generation Proteasome Inhibitors

1.1.1. Carfilzomib

Carfilzomib is an intravenously administered drug which irreversibly inhibits the chymotrypsin-like proteasome, causing inhibition of proliferation and apoptosis [6]. It was approved for relapsed MM in the United States in 2012 and by the European Commission in 2015.

In the ENDEAVOR trial, 929 patients with relapsed multiple myeloma were randomized to carfilzomib and dexamethasone versus bortezomib and dexamethasone [7]. About half of the patients were over the age of 65 (52% in the carfilzomib group and 55% in the bortezomib group). Over 90% of the patients in each group had an Eastern Cooperative

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Table 1
Key study eligibility and population characteristics relevant to older adults.

	Study	ENDEAVOR [7]	ASPIRE [8]	TOURMALINE [13]	ELOQUENT [19]	CASTOR [21]	POLLUX [22]	SIRIUS [31]
Population	Regimens	Kd vs Bd	Rd ± K	RD ± I	Rd ± Elo	Bd ± Dara	Rd ± Dara	Dara
	Proportion older patients	38.0% 65–74 15.4% ≥75	37.5% 65–74 12.1% ≥75	52% >65	Median age 66 (range 37–91)	36.7% 65–74 11.6% ≥75	40.8% 65–74 11.2% ≥75	34% 65–74 11% ≥75
	ECOG Performance Status 0–1	93%	90.5%	94%	91%	NR	95%	92%
Treatment adjustment	Dexamethasone dose adjustments	None	None	None	May be split over 2 days	Allowed dose reduction of dexamethasone for age > 75, BMI < 18.5 or poorly controlled DM	Allowed dose reduction of dexamethasone for age > 75 or BMI < 18.5	Not applicable
Eligibility criteria	Renal function exclusion	CrCl < 15 ml/min	CrCl < 50 ml/min	CrCl < 30 ml/min	CrCl < 30 ml/min	GFR < 20 ml/min/1.73m^2	CrCl ≤ 30 ml/min	GFR < 20 ml/min/1.73m^2
	Cardiac exclusions	LVEF <40%; MI within 4 months; NYHA Class 3–4 CHF	MI within 4 months; NYHA Class 3–4 CHF	MI within 6 months; unstable angina; symptomatic CHF	MI within 6 months; unstable angina or NYHA Class 3–4 CHF; uncontrolled hypertension or arrhythmia	MI within 6 months; unstable angina; NYHA Class 3–4 CHF; Grade 2 or greater arrhythmia; QTc > 470 msec	MI within 6 months; unstable angina; NYHA Class 3–4 CHF; Grade 2 or greater arrhythmia; QTc > 500 msec	MI within 1 year; Uncontrolled or unstable angina; Class 3–4 CHF
	Pulmonary exclusions	None specified	None specified	None specified	None specified	COPD with FEV1 < 60% predicted; Asthma	COPD with FEV1 < 60% predicted; Asthma	COPD; Asthma

B, bortezomib; d, dexamethasone; dara, daratumumab; R, lenalidomide; K, carfilzomib;I, ixazomib elo, elotuzumab; ECOG, Eastern Cooperative Oncology Group; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; CHF, congestive heart failure; MI, myocardial infarction; COPD, chronic obstructive pulmonary disease; CrCl, creatinine clearance' GFR, glomerular filtration rate.
NR, not reported.

Oncology Group (ECOG) performances status of 0–1. Patients with a creatinine clearance <15 ml/min or cardiac comorbidities as detailed in Table 1 were excluded. There were no planned dose adjustments of therapy for patient-specific factors. The median progression free survival in the carfilzomib group was 18.7 months vs 9.4 months in the bortezomib group [hazard ratio 0.53 (95% confidence intervals 0.44–0.65, p < 0.0001)]. This benefit was consistent in preplanned subgroup analyses of patients aged 65–74 [hazard ratio 0.53 (95% confidence intervals 0.38–0.73)] and patients aged 75 and older [hazard ratio 0.38 (95% confidence intervals 0.23–0.65)]. The rate of serious adverse events (SAEs) in the carfilzomib group was 48% versus 36% in the bortezomib group. Subgroup analyses of adverse events by age were not provided.

In the phase III ASPIRE trial, 792 patients with relapsed multiple myeloma were randomized to carfilzomib, lenalidomide and dexamethasone vs lenalidomide and dexamethasone alone [8]. Nearly half (49.6%) of the patients were age 65 or older. More than 90% had a good performance status (ECOG PS 0–1). Patients with a creatinine clearance <50 ml/min or cardiac comorbidities were excluded (Table 1). No initial dose adjustments were planned related to patient-specific factors. The carfilzomib group experienced a superior progression free survival compared with the control group [26.3 months vs 17.6 months, hazard ratio 0.69 (95% confidence intervals 0.57–0.83, p = 0.0001)]. The benefit was consistent in the preplanned subset analysis of individuals aged 65 and older. The rates of grade 3 or greater toxicities were similar in the two treatment groups (83.7% in the carfilzomib group vs 80.7% in the control group); notable toxicities that occurred more frequently in the carfilzomib group included cough, upper respiratory infections, fever, diarrhea and hypertension. No analysis of toxicities by age was presented.

Several recent studies have raised concerns about the risk of cardiac toxicity, which is particularly relevant in older adults who may have underlying cardiac comorbidities. In one analysis of over 500 patients with relapsed MM who received carfilzomib on a series of Phase II trials, 22% experienced cardiac adverse events (9.5% grade 3 or greater) [9]. Events did not appear to be related to cumulative carfilzomib dose, as the occurrence of events did not increase with later cycles. In another cohort study, 12% of patients who received carfilzomib experienced a drop in their ejection fraction (EF) of 20% or greater [10]. The only cardiovascular risk factor associated with cardiac events was peripheral artery disease. The reduction in EF was reversible with dose interruption and dose reduction. In another cohort study, 10% of patients had a decrease in their EF, but most had another potential explanation for the decline, resulting in a 3% incidence of decreased EF clearly attributable to carfilzomib [11]. In sum, the incidence of and risk factors for cardiac adverse events in older adults with comorbidities requires additional study.

Several ongoing trials will specifically examine the role of carfilzomib in older adults with newly diagnosed multiple myeloma, yielding greater insight into the risks and benefits in this population. In one phase II trial [IFM2012-03 (NCT02302495)], patients aged 65 years and older will receive weekly carfilzomib in combination with melphalan and prednisone. In a phase I/II study (NCT02204241), older adults (≥65 years) with newly diagnosed multiple myeloma will receive carfilzomib, cyclophosphamide and dexamethasone.

1.1.2. Ixazomib

Ixazomib is an orally administered therapy which reversibly inhibits the chymotrypsin-like activity of the proteasome, inducing accumulation of ubiquitinated proteins, inducing apoptosis [12]. In the United States, ixazomib was FDA approved in combination with lenalidomide for relapsed myeloma in 2015. The European Commission granted conditional authorization in the same combination in November, 2016.

In the TOURMALINE-MM1 trial, 772 patients with relapsed or refractory myeloma were randomized to receive either ixazomib, lenalidomide and dexamethasone (IRd) or placebo, lenalidomide and dexamethasone (Rd) [13]. The median age of the entire group was 66 (range 30–91) Most patients had a good performance status (ECOG PS 0-1); only 6%