At what point are we on the way to optimally treat multiple myeloma patients over 75 years of age in 2023?

Agata Tyczyńska[A–F], Jan Zaucha[A,C–F]

Department of Hematology and Transplantology, University Clinical Center, Medical University of Gdańsk, Poland

A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
D – writing the article; E – critical revision of the article; F – final approval of the article

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Address for correspondence
Jan Zaucha
E-mail: jan.zaucha@gumed.edu.pl

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Abstract

Several novel drugs for multiple myeloma, including monoclonal and bispecific antibodies, immunomodulatory agents, and newer-generation proteasome inhibitors, have been introduced over the last decade. Based on the results of randomized clinical trials, the drugs have been incorporated into current treatment recommendations, with the most substantial changes observed in patients under the age of 75. However, new therapeutic options have been indirectly proposed for patients over 75, despite the lack of conclusive data from randomized prospective trials. This paper outlines the development of myeloma therapy and summarizes the current treatment recommendations for patients over 75 by systematically reviewing the most crucial studies involving this group of individuals, with a focus on evaluating treatment safety and efficacy. Melphalan–prednisone (MP), bortezomib plus MP (VMP), lenalidomide–dexamethasone (Rd), and bortezomib plus Rd (VRd) regimens have evolved over the past few years as therapies of choice for the first-line treatment of these patients. A breakthrough came with daratumumab, which increased response rates, extended median progression-free survival (PFS) and overall survival (OS) in the absence of significantly increased toxicity when added to the above regimens.

Key words: multiple myeloma, elderly, frailty, daratumumab, over 75 years of age

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Background

Multiple myeloma patients over 75 years of age are an eminently heterogeneous group, ranging from very frail to relatively fit and independent. Tolerance of oncological treatments decreases with age and, as one ages, the presence of additional burdens, such as comorbidities, reduced compensatory capacity of internal organs, slower recovery, lower tolerance to adverse effects, simultaneous use of multiple drugs, psychomotor limitations, and less physical activity, develop. For these reasons, potential therapeutic options in this group of patients are limited. In addition, it is very difficult to predict individual tolerance to planned treatments. Myeloma-dedicated frailty status indices, such as the Myeloma Frailty Score, are helpful in treatment planning. Defining the intensity of treatment for an elderly myeloma patient should not only depend on the risk of the disease but also require an assessment of the mental, social and physical condition, an estimation of the life expectancy of the patient with and without myeloma, and predicting how the treatment and disease impact the patient's quality of life. Therefore, the goal of therapy in this group of patients is not only to achieve a profound response and extend time free from disease progression but also to maintain intellectual and physical independence. The treatment of the elderly often requires a third person in terms of availability and organization of care.[1–11]

Objectives

This literature review encompasses the available results of clinical trials published from 1960 to 2022 that involved patients over 75 years of age. An attempt was made to propose practical guidelines for clinicians on individualizing therapy in these patients in order to safely achieve the longest possible survival time with a preserved quality of life.

Epidemiology

Multiple myeloma accounts for approx. 13% of hematologic malignancies and 2% of all cancers in humans.[2–4] Among the most common lymphoid tissue neoplasms, multiple myeloma is 2nd to chronic lymphocytic leukemia,[1–3,8,9] and is one of the most common indications for hospitalization in hematology departments.[2,3]

Multiple myeloma incidence increases with age, though its occurrence rates are influenced by increasing accessibility to a faster and earlier diagnosis.[2–5,8] The highest incidence rates are observed in Australia and New Zealand (age-standardized incidence rates of 37.7/100,000 for males and 29.4/100,000 for females) and North America (16.4/100,000 for males and 11.7/100,000 for females), and the lowest in Asia (0.2/100,000 for both males and females in China), while in Europe the incidence rate is at 4.5–6/100,000. The incidence rate observed in Poland is similar to the European one: 4.36/100,000, including 4.84 for males and 3.89 for females.[8,9] The median age at diagnosis is 70 years,[1–4,9] with more than 60% of patients over 65 and approx. 32–38% over 75 years of age.[6,7] The indications for treating multiple myeloma in elderly patients are the same as for younger patients. According to the International Myeloma Working Group (IMWG) guidelines, initiating treatment requires that symptomatic multiple myeloma is diagnosed along with Calcium Renal Anemia Bone (CRAB) symptoms with a score of 1–4 points, or one of the following changes are found in laboratory tests (so-called SLiM-Sixty, Light Chain, magnetic resonance imaging (MRI) criteria: points 5–7)[1]:

1. Hypercalcemia: serum calcium ≥1 mg/dL over the normal upper limit or >11 mg/dL (sign C);
2. Occurrence of renal failure associated with myeloma: creatinine >2 mg/dL or a glomerular filtration rate (GFR) <40 mL/min (sign R);
3. Anemia defined as a hemoglobin concentration of 2 g/dL below the normal lower limit or <10 g/dL (sign A);
4. Presence of bone disease in the course of myeloma (a minimum of 1 osteolytic focus detected by positron emission tomography (PET) or computed tomography (CT)) (sign B);
5. The percentage of clonal plasma cells in the bone marrow ≥60%;
6. A clonal to non-clonal light chain ratio >100, with a clonal light chain concentration of at least 100 mg/L;
7. Presence of at least 2 focal lesions on MRI of a minimum of 5 mm.

Treatment of elderly patients

The challenge in choosing the optimal treatment is to tailor it to the individual biology of the disease and the patient's general condition. The first regimen used to treat multiple myeloma in elderly patients and those ineligible for an autotransplantation procedure was the melphalan–prednisone (MP) regimen, which has been in use since the 1960s.[12] The addition of the first immunomodulatory drug, thalidomide, to the MP regimen (MPT) in 1999 increased progression-free survival (PFS) by approx. 6 months (from 18.5 to 24.1 months), and was based on a meta-analysis of 5 clinical trials (Table 1)[13–19] that demonstrated overall survival (OS) to be prolonged by approx. 15 months.[14] However, the improved treatment results were burdened by more than a 2.5-fold higher rate of grade 3 and 4 non-hematologic complications, mainly related to the use of thalidomide (the recommended dose at the time was as high as 200 mg/day), thromboembolic complications, peripheral polyneuropathies, lethargy, and skin lesions.[13,14,19] The incidence of thromboembolic events was reduced in the GIMEMA and HOVON 49 trials

Table 1. Characteristics of registration trials for the melphalan–prednisone–thalidomide and melphalan–prednisone regimens for people aged over 75 years

Characteristics	Study group				
	GIMEMA	HOVON	IFM-II	NMSG	TMSG
Name of the study, reference	GIMEMA[18]	HOVON 49[15]	IFM01/01[17]	NMSG12[19]	TMSG[16]
Country/region	Italy	The Netherlands, Belgium	France	Northern Europe	Turkey
Number of patients	331	333	229	357	114
Years of recruitment	2002–2005	2002–2007	2002–2006	2002–2007	2006–2009
Age [years]	>65	>65	>75	>65	>55
Patients ≥75 years of age, n (%)	110 (33%)	121 (36%)	227 (99%)	159 (45%)	36 (31%)
Advancement, according to Durie–Salmon staging	II, III	Ib, II, III	II, III, and I high-risk	I–III symptoms	I–III symptoms
WHO status (ECOG)	0–4	0–3	0–4	0–4	0–2
Placebo	no	no	yes	yes	no
Dose of melphalan	4 mg/m^2 day 1–4	0.25 mg/kg day 1–5	0.20 mg/kg day 1–4	0.25 mg/kg day 1–4	9 mg/m^2 day 1–4
Dose of prednisone	40 mg/m^2 day 1–7	1 mg/kg day 1–5	2 mg/kg day 1–4	100 mg day 1–4	60 mg/m^2 day 1–4
Number of cycles/cycle length [weeks]	6/4	8/4	12/6	up to the plateau period/6	8/6
Thalidomide [mg/day]	100	200	100	200–400	100
Duration of treatment	until progression	8 cycles	12 cycles	until progression	8 cycles
Shift to MPT from MP	no	no	no	no	18%
Median OS MP vs. MPT [months]	47.6 vs. 45	31 vs. 40	29.1 vs. 44	32 vs. 29	26 vs. 28
Median PFS MP vs. MPT [months]	14.5 vs. 21.8	11 vs. 15	24.1 vs. 29	14 vs. 15	N/A

ECOG – Eastern Cooperative Oncology Group; MP – melphalan–prednisone; MPT – melphalan–prednisone–thalidomide; OS – overall survival; WHO – World Health Organization; N/A – not applicable.

by acetylsalicylic acid or low-molecular-weight heparin (2% to 3%) prophylaxis.[13,17] The IFM 01/01 study confirmed the safety and efficacy of the MPT regimen in patients older than 75, showing a prolonged median OS for MPT (44 months) compared to MP (29.1 months),[14,20] and it has been the recommended regimen in this age group since 2002.

In view of the relatively high toxicity of the 3-drug MPT regimen, an attempt was made to compare the 2-drug MP regimen to the thalidomide with dexamethasone (TD) regimen[20–24] in elderly patients (trial No. NCT00205751). However, OS and PFS were shorter, despite achieving better responses in the experimental TD arm (19.8 months and 16.7 months compared to 41.3 months and 20.7 months for MP). In addition, the number of complications such as thromboembolic events, polyneuropathy, fatigue, infections, psychiatric disorders, and constipation was higher for the TD arm, mainly in patients over 75, which was probably related to the high doses of thalidomide and dexamethasone (the average dose administered was 200 mg/day of thalidomide and 40 mg of dexamethasone for the first 4 days of the cycle). The results indicated that the 3-drug regimen was more effective in older patients, but it was at the expense of greater toxicity, so the choice of the optimal treatment was still an open question.

New opportunities to determine optimal treatment in the elderly were created in 2005 with the registration of lenalidomide, a 2nd-generation immunomodulatory drug with less toxicity, especially in polyneuropathy and thrombotic events. The MM-015 trial, performed in patients over 65 and ineligible for transplantation, compared 3 regimens, namely MP, melphalan, prednisolone and lenalidomide (MPR) and MPR in the induction phase and maintenance treatment (MPR-R).[22,25,26] The induction phase included 9 cycles of 28 days. The primary study endpoint was achieved, and there was a marked improvement in median PFS time with the MPR-R regimen (≥31 months) compared to MPR (14 months) and MP (13 months). The MPR regimen outperformed MP as an induction regimen in terms of response rate, quality of response and overall response rate. However, in patients older than 75, the median time of PFS for MPR-R was 19 months, for MPR – 12 months, and for MP – 15 months. The failure to demonstrate better efficacy using MPR in this age group may have been due to an increased incidence of adverse effects, particularly hematologic toxicity, which was associated with a more frequent need for dose modifications. The most important observation of this study was that maintenance treatment with lenalidomide (10 mg) alone, administered on days 1 to 21 over a 28-day cycle, was associated with improvements in PFS regardless of age

(median PFS time of 31 months, and 19 months for patients >75 years old) and an acceptable rate of hematologic adverse events in the form of asymptomatic cytopenias.

Another attempt aimed at determining the optimal treatment in elderly patients was made during the EMN01 trial between 2009 and 2012, which randomized newly diagnosed myeloma patients aged over 65 to 3 treatment arms: lenalidomide–dexamethasone (Rd), MPR, and cyclophosphamide, lenalidomide and prednisone (CRP).[25] The PFS time after a 31-month follow-up period was 23 months for Rd, 27 months for MRP and 23 months for CPR (Rd compared to MPR, p = 0.216; Rd compared to CPR, p = 0.872; MPR compared to CPR, p = 0.148), while the PFS time in the subgroup of patients older than 75 was 22 months for Rd, 18 months for MPR and 21 months for CPR (Rd compared to MPR, p = 0.572; Rd compared to CPR, p = 0.699; MPR compared to CPR, p = 0.914).[26] Adding an alkylating drug (melphalan or cyclophosphamide) to the lenalidomide and steroid combination showed no benefit in terms of PFS time in all patients. In contrast, the MPR regimen was burdened with a more than 60% rate of hematologic complications.[26,27] The above study clearly indicated that the 3-drug treatment is recommended for younger patients and that the optimal treatment approach for patients aged >75 years is a 2-drug regimen, such as lenalidomide plus a steroid. However, the decision over which type of steroid to use (dexamethasone in lower doses (20 mg once a week) or appropriately dosed prednisone) remained an unresolved issue.[26–28]

The NCT00098475 study provided important guidance on the treatment of the elderly, and its main goal was to identify the optimal dose of dexamethasone combined with lenalidomide. Two 28-day, 2-drug regimens of lenalidomide with dexamethasone were compared, with 1 arm receiving high doses of dexamethasone (40 mg for 4 days with 4 days off) and the other receiving 40 mg every 7 days. The lenalidomide dosage was 25 mg in both arms. The study was terminated early due to the significant safety advantage of lower doses of dexamethasone. High doses of dexamethasone yielded higher response rates for complete remission and had a very good partial response; however, this did not result in an improved PFS time. Indeed, the median PFS time for the high dose was 19.1 months (15.7–26.3), while the low dose resulted in PFS time of 25.3 months (22.3 – not reached, p = 0.026),[26] and there was no correlation between the depth of response and the length of response. However, the trial was stopped after 1 year due to the better OS achieved with low-dose dexamethasone compared to the high dose. Nonetheless, it should be remembered that in certain cases, such as acute renal failure due to myeloma nephropathy, myeloma cord compression or aggressive refractory disease, high-dose steroids still play an important role in therapy.

Based on the results of the study outlined above, the Frontline Investigation of Lenalidomide + Dexamethasone versus Standard Thalidomide Trial-MM-020/IFM 07 01 (FIRST) study was designed for patients over 65 years of age and compared MPT (12 cycles of 42 days), Rd (18 cycles, Rd18) and Rd continuous regimens until disease progression (Table 2). In the Rd arms, doses of lenalidomide (25 mg) and dexamethasone (40 mg) were administered on days 1, 8, 15, and 22. Approximately 1/3 of the study participants were older than 75 years.[28,29] After 3 years of follow-up, the median PFS was 26 months for the Rd continuous regimen, 21 months for Rd18, and 21.9 months for MPT. Meanwhile, the median OS time was 59.1 months for the Rd continuous arm, 62.3 months for Rd18, and 49.1 months for MPT. The highest rate of hematologic complications was observed with the MPT regimen (45%).[30] The most important achievement of this study was that it demonstrated the highest efficacy in terms of the number of achieved responses (overall response rate (ORR) = 75.1%) and the duration of response in patients older than 75. As such, the Rd continuous regimen extended the time to 2nd progression or death to 35 months, prolonged PFS to 26 months, and significantly increased OS to 59 months. Since publishing the results of the FIRST study, the Rd continuous regimen has been the recommended treatment for patients ineligible for autologous transplantation and the elderly. A significant advantage of this treatment option is the oral route of drug administration.

Unfortunately, the Rd regimen is not sufficiently effective in all elderly patients. Therefore, attempts have been made to determine the role of proteasome inhibitors in treating this group. Bortezomib was the first effective proteasome inhibitor and is still recommended for the treatment of both younger and older patients.[1] Its main advantage over lenalidomide is the lack of nephrotoxicity, though it induces polyneuropathy in some patients, which is not dose-dependent, as with thalidomide. The VISTA study compared bortezomib plus MP (VMP) and MP regimens, with 30% of patients being over 75 years of age.[29–31] Median PFS was prolonged to approx. 22 months in the VMP arm compared to 16.6 months in the MP arm (Table 2).[28–40] However, better PFS outcomes were burdened by a higher number of non-hematologic adverse events, mainly peripheral polyneuropathy. Subsequent studies evaluating the safety and efficacy of multidrug regimens using bortezomib for transplant-ineligible patients (VMP and bortezomib, thalidomide dexamethasone (VTd)), namely the GIMEMA BIW, GIMEMA Q7 and GEM2005MAS655 trials (in all studies, patients over 75 years of age accounted for 30%, 26% and 32%, respectively), demonstrated the same efficacy. The VISTA (21.7 months), GIMEMA BIW (25.2 months), GIMEMA QW (22.2 months), and GEM2005MAS65 trials (38 months) reported an increased median PFS, which was associated with once-weekly bortezomib maintenance treatment for up to 3 years instead of twice-weekly administration.[40] The peripheral neuropathy (grade 3 and 4) incidence in the VISTA study was 13%, 14% in the GIMEMA BIW trial, 7% in the GEM2005MAS65 trial, and 2% in the GIMEMA QW trial.[41]

Table 2. Registration trials of currently used treatment regimens

Name of the study, year	Regimens used	Regimen details	Median progression-free survival (mPFS) [months]	Median overall survival (mOS) [months]
VISTA, 2008[29]	VMP 9 cycles, 42 days	bortezomib: 1.3 mg/m^2 IV; days 1, 4, 8, 11, 22, 25, 29, 32 (cycles 1–4); days 1, 8, 22, 29 (cycles 5–9)	24	56.4
	MP 9 cycles, 42 days	melphalan: 9 mg/m^2; days 1–4 prednisolone: 60 mg/m^2; days 1–4; continuous	18	43
FIRST, 2014[27,28,30]	Rd continuous, 28 days	28-day regimen: lenalidomide: 25 mg; days 1–21 dexamethasone: 40 mg; days 1, 8, 15, 22	26	59.1
	Rd 18 cycles, 28 days	lenalidomide: 25 mg; days 1–21 dexamethasone: 40 mg; days 1, 8, 15, 22	21	62.3
	MPT 12 cycles, 42 days	melphalan: 0.25 mg/kg; days 1–4 prednisolone: 2 mg/kg; days 1–4 thalidomide: 200 mg daily	21.9	49.1
UPFRONT, 2015[31]	VD 8 cycles, 21 days	bortezomib: 1.5 mg/m^2 IV; days 1, 4, 8, 11 dexamethasone: 20 mg; days 1, 2, 4, 5, 8, 9, 11, 12 (cycles 1–4); days 1, 2, 4, 5 (cycles 5–8)	14.7	49.8
	VTd 8 cycles, 21 days	bortezomib: 1.5 mg/m^2 IV; days 1, 4, 8, 11 dexamethasone: 20 mg; days 1, 2, 4, 5, 8, 9, 11, 12 (cycles 1–4); days 1, 2, 4, 5 (cycles 5–8) thalidomide: 100 mg; days 1–21	15.4	51.5
	VMP 8 cycles, 21 days; maintenance with bortezomib IV 1.5 mg/m^2, days 1, 8, 15, 22	bortezomib: 1.5 mg/m^2 IV; days 1, 4, 8, 11 prednisolone: 60 mg/m^2; days 1–4 melphalan: 9 mg/m^2; days 1–4	17.3	53.1
SWOG SO7777, 2017[34]	VRd 8 cycles, 21 days	bortezomib: 1.3 mg/m^2 IV; days 1, 4, 8, 11 lenalidomide: 25 mg; days 1–14 dexamethasone: 20 mg; days 1, 2, 4, 5, 8, 9, 11, 12	43	75
	Rd 6 cycles, 28 days	lenalidomide: 25 mg; days 1–21 dexamethasone: 40 mg; days 1, 8, 15, 22	30	64
CLARION, 2019[35]	KMP 9 cycles, 42 days	carfilzomib: 20 mg/m^2 IV on days 1 and 2 in cycle 1, 36 mg/m^2 IV in others; days 1, 2, 8, 9, 22, 23, 29, 30 melphalan: 9 mg/m^2; days 1–4 prednisolone: 60 mg/m^2; days 1–4	22.3	no data
	VMP 9 cycles, 42 days	bortezomib: 1.3 mg/m^2 SC or IV on days 1, 4, 8, 11, 22, 25, 29, 32 (cycles 1–4); days 1, 8, 22, 29 (cycles 5–9) melphalan: 9 mg/m^2; days 1–4 prednisolone: 60 mg/m^2; days 1–4	22.1	no data
ALCYONE, 2018[37,38]	DaraVMP 9 cycles, 42 days	daratumumab: 16 mg/kg IV/week in cycle 1; every 3 weeks until cycle 29, then every 4 weeks bortezomib: 1.3 mg/m^2 SC or IV on days 1, 4, 8, 11, 22, 25, 29, 32 (cycles 1–4); days 1, 8, 22, 29 (cycles 5–9) melphalan: 9 mg/m^2; days 1–4 prednisolone: 60 mg/m^2; days 1–4	not reached	under evaluation
	VMP 9 cycles, 42 days	bortezomib: 1.3 mg/m^2 SC or IV on days 1, 4, 8, 11, 22, 25, 29, 32 (cycles 1–4); days 1, 8, 22, 29 (cycles 5–9) melphalan: 9 mg/m^2; days 1–4 prednisolone: 60 mg/m^2; days 1–4	19.3	under evaluation
MAIA, 2019[36]	Dara-Rd 28-day cycles	daratumumab: 16 mg/kg IV/week (cycles 1 and 2); every 2 weeks (cycles 3–6); then every 4 weeks lenalidomide: 25 mg; days 1–21 dexamethasone: 40 mg weekly	not reached	under evaluation
	Rd continuous, 28-day cycles	lenalidomide: 25 mg; days 1–21 dexamethasone: 40 mg weekly	31.9	under evaluation
TOURMALINE-MM2[32,39]	IRd 9 cycles, 28 days	ixazomib: 4 mg; days 1, 8, 15 lenalidomide: 25 mg; days 1–21 dexamethasone: 40 mg; days 1, 8, 15, and 22 (20 mg for patients >75 years old)	35.3	no data
	Rd 9 cycles, 28 days	lenalidomide: 25 mg; days 1–21 dexamethasone: 40 mg; days 1, 8, 15, and 22 (20 mg for patients >75 years old)	21.8	no data
VRd lite, 2014[33]	VRd 35 days	bortezomib: 1.3 mg/m^2 IV; days 1, 8, 15, 22 lenalidomide: 15 mg; days 1–21 dexamethasone: 20 mg; days 1, 2, 8, 9, 15, 16, 22, 23	35.1	not reached

MP – melphalan–prednisone; VMP – bortezomib plus MP; Rd – lenalidomide–dexamethasone; MPT – melphalan–prednisone–thalidomide; VTd – bortezomib–thalidomide–dexamethasone; VRd – bortezomib plus RD; KMP – carfilzomib–melphalan–prednisone; IV – intravenous; SC – subcutaneous; VD – bortezomib–dexamethasone; IRd – Ixazomib–lenalidomide–dexamethasone.

The UPFRONT trial, dedicated to determining the role of bortezomib in the treatment of the elderly (half of the patients were >75 years old), randomized participants into bortezomib dexamethasone (Vd), VTd and VMP arms.[31] The median PFS time was similar for each regimen, that being 14.7 months for Vd, 15.4 months for VTd, and 17.3 months for VMP, with no significant differences in the incidence in grade 3 and 4 peripheral polyneuropathies in the Vd (24%), VTd (29%) or VMP (21%) arms.[31,34] As such, the study indicated the possibility of using a 2-drug regimen (Vd) in elderly patients, as it provided the same benefit as 3-drug regimens. However, it should be noted that it was possible to reduce the incidence of neurological complications by using bortezomib once a week.[29–31,42,43]

The above studies, similar to those evaluating lenalidomide, demonstrated the advantages of 2-drug regimens in patients over 75 years of age. However, the partners for lenalidomide and bortezomib were alkylating drugs (melphalan or Endoxan) or the relatively toxic thalidomide (VTd). In this regard, a key study in the elderly, in which patients over 75 accounted for 25.5% of participants, was the US SWOG S0777 trial comparing the bortezomib plus Rd (VRd) regimen (bortezomib, lenalidomide and dexamethasone) to the Rd regimen (lenalidomide and dexamethasone).[34] Median PFS for patients over 75 treated with VRd was 39 months, compared to 20 months for those treated with the Rd regimen ($p = 0.0037$), while the median OS time was 63 months (VRd) compared to 31 months (Rd, $p = 0.0250$) (Table 2).[34] Grade 3 adverse events occurred in 82% of patients in the VRd arm and in 75% of patients in the Rd arm. The most common hematologic adverse events attributed to the treatments were ≥grade 3 cytopenias in all 4 cell lines, and the most common ≥grade 3 nonhematologic adverse events were muscle weakness, fatigue, cardiac disorders, hyperglycemia, thrombosis, embolism, and diarrhea. As expected, neurological events graded 3 or higher, mainly peripheral polyneuropathy, were more frequent in the VRd (33%) group than in the Rd group (11%, $p < 0.0001$), though there was a balance between the 2 groups for all other events.

The SWOG 0777 study unequivocally showed improved PFS, OS, depth of response, and response rates using the VRd regimen while maintaining a relatively comparable safety profile to the Rd regimen.[34] In addition, lower toxicity and additional improvements in survival can be expected with weekly subcutaneous administration of bortezomib.[43]

The results of the presented studies indicate that it is possible to safely use a 3-drug regimen in patients over 75 years of age, as the treatment offers the greatest benefit, with long OS and relatively well-tolerated drug toxicity. The VRd appears to be the safest of the 3-drug regimens. On the other hand, the Rd regimen, in an indirect comparison with VTd and VMP, provides similar benefits with less toxicity and is a good alternative in the absence of a 3-drug regimen, mainly in the presence of contraindications to bortezomib. However, using the VRd regimen in the elderly, despite its advantages, is not appropriate for all patients, primarily due to the risk of developing polyneuropathy and causing a decline in quality of life.

An attractive proposal for improving the efficacy of the 2-drug Rd regimen was the addition of daratumumab, which has a completely different mechanism of action than the drugs used so far. Daratumumab (D) is a human monoclonal antibody of the immunoglobulin (Ig)G1 class and is effective against the cluster of differentiation (CD)38 antigen. After binding to CD38, it strongly inhibits cell growth and cell adhesion to the microenvironment and has a direct anti-tumor effect. In addition, it is highly immunologically active and uses complement-dependent cytotoxicity (CDC) to induce tumor cell lysis and tumor cell death through an effector function mediated, for example, by natural killer (NK) cells, which it activates by cross-binding with the Fc receptor (ADCC). Moreover, daratumumab induced antibody-dependent cellular phagocytosis (ADCP), in which macrophages play a major role. In addition, it exhibits immunomodulatory properties by increasing the levels of $CD4^+$ and $CD8^+$ T cells in the blood and bone marrow. The antibody also reduces the number of regulatory T cells (CD38+Tregs), B cells (CD38+Bregs) and myeloid-derived suppressor cells (CD38+MDSCs).

The comparison of the randomized MAIA Rd with the D-Rd trial, in which 43.2% of patients were over 75 years old, was crucial for results concerning older people. The median PFS time was not reached in the experimental arm after a 56-month follow-up, but it was reached in the control group after 34.4 months.[36,42,44] Furthermore, the proportion of patients who had a complete response, or better, an almost doubled response, and negative or minimal residual disease was more than 3 times higher for the daratumumab group than the control group.[36,44–49] However, reporting of grade 3 and 4 adverse events was more frequent in the daratumumab arm and included neutropenia (54% compared to 37%), pneumonia (19% compared to 11%) and lymphopenia (16% compared to 11%). Furthermore, treatment-related deaths were slightly higher in the daratumumab arm (4%) than in the control group (3%), and no new complications were observed.[36,45–49]

An alternative partner to dexamethasone, instead of Rd, is the MPV regimen, which was used in the ALCYONE trial comparing daratumumab plus VMP (D-VMP) to VMP (29.9% were patients older than 75 years).[37,38,46–48] As expected, PFS analyses showed consistent superiority of D-VMP over VMP across all subgroups, which included those over 75 years of age and prognostic factors (stage III ISS disease, renal failure or high-risk cytogenetic profile). Additionally, as in the MAIA trial, they did not reach the median PFS, but the PFS of 18.1 months was reported for the control group (values similar to the FIRST

trial).[27,28,36,50] Grade 3 and 4 hematologic complications included neutropenia (39.9% of D-VMP patients compared to 38.7% of control patients), anemia (15.9% of D-VMP patients compared to 19.8% of control patients) and thrombocytopenia (34.4% of D-VMP patients compared to 37.6% of control patients). In addition, the percentage of grade 3 and 4 infections was higher in the D-VMP group (23.1%) than in the control group (14.7%). The most frequent grade 3 or 4 infection was pneumonia, which occurred more often in the D-VMP group (11.3%) than in the control group (4.0%), while peripheral polyneuropathy was more common in the control group (34.2% compared to 28.3%), with grade 3 and 4 infections occurring at 4% for the VMP and 1.4% for the D-VMP groups. Of course, it is important to keep in mind the adverse events associated with daratumumab administration, of which grades 1 and 2 affected 1 in 4 patients, and grades 3 and 4 occurred in 4.9% of patients. However, the number and quality of daratumumab-related events have been effectively minimized, with the introduction of a subcutaneous form. The efficacy and safety of a fixed dose (1800 mg) of subcutaneous daratumumab were demonstrated in the PLEIADES trial, in which all events associated with subcutaneous daratumumab administration accounted for 7.5% (15/199), with 1 case involving grade 3 and the rest grade 1 or 2.[51] Furthermore, no drug-related events were reported with the 2nd administration, and only 3 grade 1 and 2 cases (1.5%; 3/199) were reported in subsequent administrations.

Overall toxicity did not increase when using daratumumab in combination with VMP. Except for respiratory tract infections (3 times more common in the daratumumab group), there was a balance between the daratumumab and control groups in terms of adverse events, although peripheral sensory neuropathy rates were lower in the daratumumab group. In addition, in the ALCYONE trial evaluating patients' quality of life, both arms showed early and sustained improvements in health-related quality of life (HRQoL), function and reduced disease symptoms.[37]

Both D-Rd and D-VMP regimens can be used in patients over 75 years of age, but due to toxicity, the D-Rd regimen is the safer and more convenient form of treatment. A study comparing the D-Rd regimen with VRD lite is currently being planned, the results of which may change the sequence of recommended regimens (study No. NCT05561387).

Carfilzomib is a novel selective and irreversible proteasome inhibitor recommended for refractory multiple myeloma and/or relapse. A phase I/II trial for a first-line treatment of patients over 65 years of age, combining carfilzomib with melphalan and prednisone (KMP) reported a PFS of 21 months and a response rate of 90%. The study formed the basis for the Phase 3 CLARION trial, which directly compared VMP and KMP arms. The study included 31.3% of patients over 75 years of age and confirmed the safety of carfilzomib as first-line treatment, primarily in terms of polyneuropathy incidence (incidence of minimum grade 2 polyneuropathy was 2.5% in the KMP arm and 35.1% in the VMP arm), but showed no statistical differences in PFS time (22.3 months for KMP compared to 22.1 months for VMP).[35] In contrast, the ENDURANCE trial compared VRd to carfizomib, lenalidomide and dexamethasone (KRd). The study included 32% of patients over 70 years of age and showed no increase in PFS time after carfilzomib treatment. The regimen was more toxic in this group of patients.[52]

Ixazomib is an oral proteasome inhibitor (like 2nd-generation carfilzomib) that was studied in the first-line treatment of transplant-ineligible patients (those over 75 years of age accounted for 43.5%). The TOURMALINE-MM2 study compared ixazomib in combination with Rd to Rd alone, and the results suggested a clinically significant PFS benefit for this group of patients, with a median PFS in the ixazomib arm of 27.9 months and 20.5 months for Rd, and a hazard ratio (HR) of 0.87, but this was not statistically significant.[39] The PFS benefit of ixazomib-Rd was observed primarily in patients with renal failure, high-risk cytogenetics and grade 3 injury severity score (ISS). Furthermore, the toxicity profile was acceptable but markedly higher in the ixazomib group, though it did not reduce the patient's quality of life, with rash and diarrhea grade 3 and above being more common in the investigational regimen group. The ixazomib regimen in combination with Rd may be considered in patients who can only take oral medications, are high-risk, or those with renal failure.

Studies evaluating the safety and efficacy of regimens combining lenalidomide and dexamethasone with ixazomib, elotuzumab, isatuximab, bispecific antibodies, or chimeric antigen receptor (CAR)-T therapy for first-line treatment are currently underway, and some studies may include patients aged over 75.

The results of the CAR-T therapies, namely idecabtagene vicleucel (ide-target) and ciltacabtagene autoleucel (ciltacel), both targeting the myeloma B-cell maturation antigen (BCMA), are eagerly awaited. Both therapies are undergoing intensive first-line trials in transplant-ineligible patients, such as CARTITUDE 5. However, patients over 80 are not included in the study (NCT04923893). Bispecific antibodies, on the other hand, are most often administered subcutaneously cyclically (every 1–4 weeks) and do not require time-consuming production for each patient. For this antibody (bispecific antibodies), one target is CD3 on T cells, and the other is an antigen found on myeloma cells such as BCMA (teclistamab, elranatamab, linvoseltamab), GPRC5D (talquetamab) and FcRH5 (cevostamab). Importantly, the trials on teclistamab and elranatamab (EudraCT No. 2021-000803-20) for non-transplant patients as first-line treatment have recently been started, with no age limit.[53] The most serious complications of both therapies are infectious complications accompanied by hypogammaglobulinemia, cytokine release syndrome (CRS) and neurological disorders (ICONS). From the data

obtained so far, the percentage of grade 3 and 4 complications is acceptable.

Patients over 75 have the highest mortality rate, which did not significantly improved in the analysis up to 2012.[54] Factors that increase the risk of death, along with early death (up to 12 months after the diagnosis of the disease), include limited function according to the Eastern Cooperative Oncology Group (ECOG) status,[55–57] advanced disease (ISS 3), and comorbidities such as cardiovascular diseases, including hypertension and chronic kidney disease.[58–60] In a retrospective meta-analysis of 4 randomized trials, it was shown that patients older than 75 have an increased risk of death (HR: 1.44, 95% confidence interval (95% CI): 1.20–1.72, $p < 0.001$).[44] Additionally, the aggressiveness of the therapy contributes to this state of affairs. Indeed, there was a 3.02-fold increase in patients receiving VTd/bortezomib–melphalan–prednisone–thalidomide (VMPT), a 1.62-fold increase in patients receiving VMP, and a slight increase in those receiving MP/MPT.[20,21,41,50,61]

Conclusions

The treatment of multiple myeloma patients, including elderly patients over 75 years of age, has undergone significant changes over the past 20 years. The MPT regimen based on the FIRST trial, which was groundbreaking in the early 2000s, has been replaced by the Rd regimen. The VRd 3-drug regimen, its "light" version in particular, has been considered an equally interesting option. However, based on the ALCYONE and MAIA trials, the D-Rd regimen is the most effective and safest treatment option.

The Rd regimen with ixazomib did not show a significant benefit over Rd in patients over 75, although it is an attractive treatment option due to its complete ambulatory nature (all drugs are administered orally). In contrast, there are no data on the use of the Rd regimen with carfilzomib as a first-line therapy in patients over 75, as the ENDURANCE trial only included patients between the ages of 70 and 75. The only available treatment recommendations for patients over 75 are those by the National Comprehensive Cancer Network (NCCN). The NCCN panel does not recommend separate treatment for patients over 75 years of age; however, for frail patients, the VRD lite regimen is recommended.

Therapeutic decisions should be made after assessing the risk of the disease, the severity of CRAB symptoms, especially renal failure, and other comorbidities, as well as the patient's situation (place of residence, commuting, availability of care by a third person, for example). The treatment of renal failure patients who do not yet need renal replacement therapy may be a challenge, though VTd can be considered for this group. The VTd regimen may also be appropriate for patients at high risk of thromboembolism. Switching from lenalidomide to melphalan can be considered (VMP regimen based on the UPFRONT and CLARION trials).

Regimens with bortezomib are recommended for patients with high cytogenetic or thromboembolic risks, those with renal failure, and those with a contraindication to anticoagulants. The neurotoxicity of bortezomib can be reduced without affecting OS if administered once a week.[38,50,62] On the other hand, lenalidomide is indicated for patients with pre-existing polyneuropathy.

Undoubtedly, patients over 75 constitute a minority in clinical trials, and those over 80 are often ineligible for trials. Therefore, the access to clinical data collected by treatment centers is also important to build real treatment guidelines for this group of patients.

Given that age alone increases the risk of death in elderly patients, deciding on the type of therapy remains a challenge and requires further follow-up and prospective analyses.

ORCID iDs

Agata Tyczyńska https://orcid.org/0000-0002-2067-2715
Jan Zaucha https://orcid.org/0000-0002-0986-8936

References

1. Dimopoulos MA, Moreau P, Terpos E, et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2021;32(3):309–322. doi:10.1016/j.annonc.2020.11.014
2. Suska A, Jurczyszyn A. Epidemiology and etiopathogenesis of multiple myeloma and monoclonal gammapathy of undetermined significance. *Postepy Hig Med Dosw*. 2018;72:953–965. doi:10.5604/01.3001.0012.7296
3. Kyle RA, Rajkumar SV. Multiple myeloma. *Blood*. 2008;111(6):2962–2972. doi:10.1182/blood-2007-10-078022
4. Padala SA, Barsouk A, Barsouk A, et al. Epidemiology, staging, and management of multiple myeloma. *Med Sci (Basel)*. 2021;9(1):3. doi:10.3390/medsci9010003
5. Jurczyszyn A, Suska A. Multiple myeloma. In: *Reference Module in Biomedical Sciences*. Elsevier; 2019:461–478. doi:10.1016/B978-0-12-801238-3.11412-6
6. National Cancer Institute. *Cancer Stat Facts: Myeloma*. Rockville, USA: National Cancer Institute; 2021. https://seer.cancer.gov/statfacts/html/mulmy.html. Accessed October 6, 2021.
7. Polish National Cancer Registry. *Multiple Myeloma and Malignant Plasma Cell Neoplasms – 2019*. https://onkologia.org.pl/sites/default/files/Multiple_myeloma_and_malignant_plasma_cell_neoplasms.pdf.
8. Szumera-Ciećkiewicz A, Wojciechowska U, Didkowska J, et al. Population-based epidemiological data of follicular lymphoma in Poland: 15 years of observation. *Sci Rep*. 2020;10(1):14610. doi:10.1038/s41598-020-71579-6
9. Kazandjian D. Multiple myeloma epidemiology and survival: A unique malignancy. *Semin Oncol*. 2016;43(6):676–681. doi:10.1053/j.seminoncol.2016.11.004
10. Manapuram S, Hashmi H. Treatment of multiple myeloma in elderly patients: A review of literature and practice guidelines. *Cureus*. 2018;10(12):e3669. doi:10.7759/cureus.3669
11. Tuchman SA, Shapiro GR, Ershler WB, et al. Multiple myeloma in the very old: An IASIA conference report. *J Natl Cancer Inst*. 2014;106(5):dju067. doi:10.1093/jnci/dju067
12. Alexanian R, Haut A, Khan A, et al. Treatment for multiple myeloma: Combination chemotherapy with different melphalan dose regimens. *JAMA*. 1969;208(9):1680–1685. doi:10.1001/jama.1969.03160090040009
13. Palumbo A, Waage A, Hulin C, et al. Safety of thalidomide in newly diagnosed elderly myeloma patients: A meta-analysis of data from individual patients in six randomized trials. *Haematologica*. 2013;98(1):87–94. doi:10.3324/haematol.2012.067058

14. Hulin C, Facon T, Rodon P, et al. Efficacy of melphalan and prednisone plus thalidomide in patients older than 75 years with newly diagnosed multiple myeloma: IFM 01/01 trial. *J Clin Oncol*. 2009; 27(22):3664–3670. doi:10.1200/JCO.2008.21.0948
15. Wijermans P, Schaafsma M, Termorshuizen F, et al. Phase III study of the value of thalidomide added to melphalan plus prednisone in elderly patients with newly diagnosed multiple myeloma: The HOVON 49 Study. *J Clin Oncol*. 2010;28(19):3160–3166. doi:10.1200/JCO.2009.26.1610
16. Beksac M, Haznedar R, Firatli-Tuglular T, et al. Addition of thalidomide to oral melphalan/prednisone in patients with multiple myeloma not eligible for transplantation: Results of a randomized trial from the Turkish Myeloma Study Group. *Eur J Haematol*. 2011;86(1):16–22. doi:10.1111/j.1600-0609.2010.01524.x
17. Ludwig H, Hajek R, Tóthová E, et al. Thalidomide-dexamethasone compared with melphalan-prednisolone in elderly patients with multiple myeloma. *Blood*. 2009;113(15):3435–3442. doi:10.1182/blood-2008-07-169565
18. Palumbo A, Bringhen S, Liberati AM, et al. Oral melphalan, prednisone, and thalidomide in elderly patients with multiple myeloma: Updated results of a randomized controlled trial. *Blood*. 2008; 112(8):3107–3114. doi:10.1182/blood-2008-04-149427
19. Waage A, Gimsing P, Fayers P, et al. Melphalan and prednisone plus thalidomide or placebo in elderly patients with multiple myeloma. *Blood*. 2010;116(9):1405–1412. doi:10.1182/blood-2009-08-237974
20. Fayers PM, Palumbo A, Hulin C, et al. Thalidomide for previously untreated elderly patients with multiple myeloma: Meta-analysis of 1685 individual patient data from 6 randomized clinical trials. *Blood*. 2011;118(5):1239–1247. doi:10.1182/blood-2011-03-341669
21. Palumbo A, Falco P, Corradini P, et al. Melphalan, prednisone, and lenalidomide treatment for newly diagnosed myeloma: A report from the GIMEMA – Italian Multiple Myeloma Network. *J Clin Oncol*. 2007;25(28):4459–4465. doi:10.1200/JCO.2007.12.3463
22. Palumbo A, Magarotto V, Bringhen S, et al. A randomized phase 3 trial of melphalan-lenalidomide-prednisone (MPR) or cyclophosphamide-prednisone-lenalidomide (CPR) vs lenalidomide plus dexamethasone (Rd) in elderly newly diagnosed multiple myeloma patients. *Blood*. 2013;122(21):536. doi:10.1182/blood.V122.21.536.536
23. Palumbo A, Hajek R, Delforge M, et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. *N Engl J Med*. 2012; 366(19):1759–1769. doi:10.1056/NEJMoa1112704
24. Magarotto V, Bringhen S, Musto P, et al. Doublet vs triplet lenalidomide-containing regimens in newly diagnosed myeloma patients, younger or older than 75 years: Subgroup analysis of a phase III study. *Blood*. 2014;124(21):2110. doi:10.1182/blood.V124.21.2110.2110
25. Bringhen S, Offidani M, Musto P, et al. Long-term outcome of lenalidomide-dexamethasone (Rd) vs melphalan-lenalidomide-prednisone (MPR) vs cyclophosphamide-prednisone-lenalidomide (CPR) as induction followed by lenalidomide-prednisone (RP) vs lenalidomide (R) as maintenance in a community-based newly diagnosed myeloma population: Updated analysis of EMN01 phase III study. *Blood*. 2017;130(Suppl 1):901. doi:10.1182/blood.V130.Suppl_1.901.901
26. Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: An open-label randomised controlled trial. *Lancet Oncol*. 2010;11(1): 29–37. doi:10.1016/S1470-2045(09)70284-0
27. Facon T, Dimopoulos MA, Dispenzieri A, et al. Initial phase 3 results of the first (Frontline Investigation Of Lenalidomide + Dexamethasone Versus Standard Thalidomide) trial (MM-020/IFM 07 01) in newly diagnosed multiple myeloma (NDMM) patients (Pts) ineligible for stem cell transplantation (SCT). *Blood*. 2013;122(21):2. doi:10.1182/blood.V122.21.2.2
28. Facon T, Dimopoulos MA, Dispenzieri A, et al. Final analysis of survival outcomes in the phase 3 FIRST trial of up-front treatment for multiple myeloma. *Blood*. 2018;131(3):301–310. doi:10.1182/blood-2017-07-795047
29. Mateos MV, Richardson PG, Schlag R, et al. Bortezomib plus melphalan and prednisone compared with melphalan and prednisone in previously untreated multiple myeloma: Updated follow-up and impact of subsequent therapy in the phase III VISTA trial. *J Clin Oncol*. 2010;28(13):2259–2266. doi:10.1200/JCO.2009.26.0638
30. Mateos MV, Bringhen S, Richardson PG, et al. Bortezomib cumulative dose, efficacy, and tolerability with three different bortezomib-melphalan-prednisone regimens in previously untreated myeloma patients ineligible for high-dose therapy. *Haematologica*. 2014; 99(6):1114–1122. doi:10.3324/haematol.2013.099341
31. Niesvizky R, Flinn IW, Rifkin R, et al. Community-based phase IIIB trial of three UPFRONT bortezomib-based myeloma regimens. *J Clin Oncol*. 2015;33(33):3921–3929. doi:10.1200/JCO.2014.58.7618
32. Stege CAM, Nasserinejad K, Van Der Spek E, et al. Efficacy and tolerability of ixazomib, daratumumab and low dose dexamethasone (Ixa Dara dex) in unfit and frail newly diagnosed multiple myeloma (NDMM) patients; Results of the interim efficacy analysis of the phase II HOVON 143 study. *Blood*. 2019;134(Suppl 1):695. doi:10.1182/blood-2019-121694
33. O'Donnell EK, Laubach JP, Yee AJ, et al. A phase 2 study of modified lenalidomide, bortezomib and dexamethasone in transplant-ineligible multiple myeloma. *Br J Haematol*. 2018;182(2):222–230. doi:10.1111/bjh.15261
34. Durie BGM, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): A randomised, open-label, phase 3 trial. *Lancet*. 2017;389(10068):519–527. doi:10.1016/S0140-6736(16)31594-X
35. Facon T, Lee JH, Moreau P, et al. Carfilzomib or bortezomib with melphalan-prednisone for transplant-ineligible patients with newly diagnosed multiple myeloma. *Blood*. 2019;133(18):1953–1963. doi:10.1182/blood-2018-09-874396
36. Facon T, Kumar SK, Plesner T, et al. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): Overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22(11):1582–1596. doi:10.1016/S1470-2045(21)00466-6
37. Mateos MV, Cavo M, Blade J, et al. Overall survival with daratumumab, bortezomib, melphalan, and prednisone in newly diagnosed multiple myeloma (ALCYONE): A randomised, open-label, phase 3 trial. *Lancet*. 2020;395(10218):132–141. doi:10.1016/S0140-6736(19)32956-3
38. Knop S, Mateos MV, Dimopoulos MA, et al. Health-related quality of life in patients with newly diagnosed multiple myeloma ineligible for stem cell transplantation: Results from the randomized phase III ALCYONE trial. *BMC Cancer*. 2021;21(1):659. doi:10.1186/s12885-021-08325-2
39. Facon T, Venner CP, Bahlis NJ, et al. Oral ixazomib, lenalidomide, and dexamethasone for transplant-ineligible patients with newly diagnosed multiple myeloma. *Blood*. 2021;137(26):3616–3628. doi:10.1182/blood.2020008787
40. Moreau P, Kolb B, Attal M, et al. Phase 1/2 study of carfilzomib plus melphalan and prednisone in patients aged over 65 years with newly diagnosed multiple myeloma. *Blood*. 2015;125(20):3100–3104. doi:10.1182/blood-2015-02-626168
41. Kuhr K, Wirth D, Srivastava K, Lehmacher W, Hellmich M. First-line therapy for non-transplant eligible patients with multiple myeloma: Direct and adjusted indirect comparison of treatment regimens on the existing market in Germany. *Eur J Clin Pharmacol*. 2016;72(3): 257–265. doi:10.1007/s00228-015-1998-5
42. Mateos MV, Oriol A, Martínez-López J, et al. Bortezomib, melphalan, and prednisone versus bortezomib, thalidomide, and prednisone as induction therapy followed by maintenance treatment with bortezomib and thalidomide versus bortezomib and prednisone in elderly patients with untreated multiple myeloma: A randomised trial. *Lancet Oncol*. 2010;11(10):934–941. doi:10.1016/S1470-2045(10)70187-X
43. Reeder CB, Reece DE, Kukreti V, et al. Once- versus twice-weekly bortezomib induction therapy with CyBorD in newly diagnosed multiple myeloma. *Blood*. 2010;115(16):3416–3417. doi:10.1182/blood-2010-02-271676
44. Bringhen S, Mateos MV, Zweegman S, et al. Age and organ damage correlate with poor survival in myeloma patients: Meta-analysis of 1435 individual patient data from 4 randomized trials. *Haematologica*. 2013;98(6):980–987. doi:10.3324/haematol.2012.075051
45. Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;375(14): 1319–1331. doi:10.1056/NEJMoa1607751

46. Palumbo A, Bringhen S, Mateos MV, et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: An International Myeloma Working Group report. *Blood*. 2015;125(13):2068–2074. doi:10.1182/blood-2014-12-615187
47. Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. *N Engl J Med*. 2016;375(8):754–766. doi:10.1056/NEJMoa1606038
48. Mateos MV, Dimopoulos MA, Cavo M, et al. Daratumumab plus bortezomib, melphalan, and prednisone for untreated myeloma. *N Engl J Med*. 2018;378(6):518–528. doi:10.1056/NEJMoa1714678
49. Facon T, Kumar S, Plesner T, et al. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. *N Engl J Med*. 2019;380(22):2104–2115. doi:10.1056/NEJMoa1817249
50. Bringhen S, Offidani M, Palmieri S, et al. Early mortality in myeloma patients treated with first-generation novel agents thalidomide, lenalidomide, bortezomib at diagnosis: A pooled analysis. *Crit Rev Oncol Hematol*. 2018;130:27–35. doi:10.1016/j.critrevonc.2018.07.003
51. Chari A, Rodriguez-Otero P, McCarthy H, et al. Subcutaneous daratumumab plus standard treatment regimens in patients with multiple myeloma across lines of therapy (PLEIADES): An open-label Phase II study. *Br J Haematol*. 2021;192(5):869–878. doi:10.1111/bjh.16980
52. Kumar SK, Jacobus SJ, Cohen AD, et al. Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): A multicentre, open-label, phase 3, randomised, controlled trial. *Lancet Oncol*. 2020;21(10):1317–1330. doi:10.1016/S1470-2045(20)30452-6
53. Martin T, Usmani SZ, Berdeja JG, et al. Ciltacabtagene autoleucel, an anti–B-cell maturation antigen chimeric antigen receptor T-cell therapy, for relapsed/refractory multiple myeloma: CARTITUDE-1 2-year follow-up. *J Clin Oncol*. 2023;41(6):1265–1274. doi:10.1200/JCO.22.00842
54. Costa LJ, Brill IK, Omel J, Godby K, Kumar SK, Brown EE. Recent trends in multiple myeloma incidence and survival by age, race, and ethnicity in the United States. *Blood Adv*. 2017;1(4):282–287. doi:10.1182/bloodadvances.2016002493
55. Krzemieniecki K. Comprehensive geriatric assessment and its clinical impact in oncology: Systematic literature review [in Polish]. *Onkol Prak Klin*. 2010;6(3):91–95. https://journals.viamedica.pl/oncology_in_clinical_practice/article/view/9204. Accessed August, 2021.
56. Lawton MP. Scales to measure competence in everyday activities. *Psychopharmacol Bull*. 1988;24(4):609–614. PMID:3074322.
57. Łacko A. Peculiarities of treatment of elderly cancer patients [in Polish]. *Old Age Med*. 2012;2(1):7–11. https://journals.viamedica.pl/medycyna_wieku_podeszlego/article/view/19209. Accessed June 21, 2021.
58. Mohty M, Cavo M, Fink L, et al. Understanding mortality in multiple myeloma: Findings of a European retrospective chart review. *Eur J Haematol*. 2019;103(2):107–115. doi:10.1111/ejh.13264
59. Xia J, Wang L, Zhou X, Wang J, Wang H, Guo H. Early mortality in elderly patients undergoing treatment for multiple myeloma in real-world practice. *J Int Med Res*. 2018;46(6):2230–2237. doi:10.1177/0300060518757640
60. Warren JL, Harlan LC, Stevens J, Little RF, Abel GA. Multiple myeloma treatment transformed: A population-based study of changes in initial management approaches in the United States. *J Clin Oncol*. 2013;31(16):1984–1989. doi:10.1200/JCO.2012.46.3323
61. Piechotta V, Jakob T, Langer P, et al. Multiple drug combinations of bortezomib, lenalidomide, and thalidomide for first-line treatment in adults with transplant-ineligible multiple myeloma: A network meta-analysis. *Cochrane Database Syst Rev*. 2019;2019(11):CD013487. doi:10.1002/14651858.CD013487
62. Cook J, Johnson I, Higgins A, et al. Outcomes with different administration schedules of bortezomib in bortezomib, lenalidomide and dexamethasone (VRd) as first-line therapy in multiple myeloma. *Am J Hematol*. 2021;96(3):330–337. doi:10.1002/ajh.26074