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Treatment of Newly Diagnosed Elderly Multiple Myeloma

Guillemette Fouquet, Francesca Gay, Eileen Boyle, Sara Bringham, Alessandra Larocca, Thierry Facon, Xavier Leleu and Antonio Palumbo

Abstract

Multiple myeloma (MM) is a disease of the elderly, with a median age at diagnosis of approximately 70 years old, and more than 30 % of patients aged >75 years. This latter and very elderly population is going to significantly rise in the near future given the increase in life expectancy in Western countries, and, most importantly, global health status of elderly patients is improving, justifying appropriate treatments. Changes in treatment paradigm from the old melphalan-prednisone regimen used since the 1970s to its use as a backbone in a nontransplant setting since the late 1990s have highlighted different subgroups in elderly MM. Some “elderly” patients could be treated like transplant eligible patients, more likely those aged between 65 and the early 70; while a second group would rather be referred to current approved treatment regimens for the non-transplant setting. A dose-intensity approach seems reasonable for this group, aiming for the best response, eventually the complete response (CR) or even minimal residual disease (MRD). The advent of novel agents such as thalidomide, bortezomib, and most recently lenalidomide have allowed a major improvement in outcome as compared to historical combinations, and soon the novel class of monoclonal antibodies should help to further improve these patients’ survival. Nonetheless, elderly patients are more

G. Fouquet · E. Boyle · T. Facon
Service des maladies du sang, Hôpital Huriez, CHRU, Lille, France

X. Leleu (✉)
Service d’Hématologie et Thérapie Cellulaire, CHU, La Milétrie, Poitiers, France
e-mail: xavier.leleu@chu-poitiers.fr

F. Gay · S. Bringham · A. Larocca · A. Palumbo
Myeloma Unit, Division of Hematology, University of Torino, Turin, Italy

29 susceptible to side effects and are often unable to tolerate full drug doses, and
30 thus require lower dose intensity regimens, or novel drugs or combinations with
31 more favourable safety profile. Recent developments in MM have focused on
32 identifying these vulnerable patients through geriatric assessment and novel
33 myeloma scoring system, including the notions of frailty, disability and
34 comorbidities. Eventually, we have reached an era in which we should be able
35 to provide individualized treatment strategies and drug doses—“tailored
36 therapy”—to improve tolerability and optimize efficacy and ultimately survival
37 for most elderly MM patients.

Keyword

39 Newly diagnosed · Elderly · Multiple myeloma
41

42 1 Introduction 43

44 Multiple myeloma (MM) is a malignant neoplasia characterized by clonal plasma
45 cell proliferation, driven by intrinsic genomic abnormalities and extrinsic bone
46 marrow stromal cell support, associated with a monoclonal protein present in the
47 blood and/or urine [1]. In Western countries, MM represents 1.5 % of all malignant
48 diseases, with an annual age-adjusted incidence of 5.6 cases per 100,000 people [2].

49 MM is a disease of the elderly: median age at diagnosis is close to 70 years, with
50 about two-third aged ≥ 65 years—including 34.8 % of patients diagnosed after
51 75 years, and 9.6 % after 85 years [2]. The number of elderly MM patients is
52 expected to increase over time, thanks to the increased life expectancy of the
53 general population, but also to the improved survival enabled by the increase use of
54 potent novel agents.

55 However, MM remains a fatal disease and its prognosis remains poor in elderly
56 patients, with a median overall survival of 24 months in patients aged over 75 years
57 at diagnosis in the US [2], and a 5-year overall survival of 26 % for the 70–79 years
58 old, and 14 % for the 80–99 year old in the UK [3]. There still is an unmet medical
59 need in this population, as early as the first relapse setting for most of them, and
60 even at diagnosis for the very elderly and frail; progress is therefore needed for
61 these patients. Still, despite the efforts in drug development and progress in
62 understanding the physiopathology of MM, management of elderly patients with
63 MM will remain challenging, because of specific clinical and biological features but
64 essentially because of frailty, comorbidities, financial, and psychosocial factors.

65 We will review current treatments, discuss various improvements in global
66 appreciation of the health status, and display future perspectives.



2 Geriatric Assessment

Frailty. A precise clinical assessment is essential when treating elderly patients, as age alone is obviously very insufficient, knowing this population is characterized by an important heterogeneity. Several studies have showed that the “in the ballpark” geriatric assessment drove to a certain failure in many elderly patients. The notion of frailty has therefore been introduced to help qualify these patients characterized by a certain risk of significant side effects during treatment—and shorter survival due to these safety issues. It is now a consensual term, but no single sign of symptom is sufficient to define it [4]. Indexes of frailty have been developed according to several factors such as weakness, poor endurance, weight loss, low physical activity, and slow gait speed. At least three factors should be present in order to define a “clinically frail elderly patient”, and the presence of this “frailty” has been identified as an independent pejorative factor in elderly adults [5]. The different degrees of frailty are summarized in Table 1.

Comorbidities also have to be taken into account, formally defined as the concurrent presence of at least two diseases diagnosed in the same person [4]. The frequency of individual chronic conditions, along with the incidence of comorbid conditions, rises with age. Comorbidity is associated with polymedication and increased risk of drug interactions. Many prognostic indices for the elderly incorporating comorbidity are available [6–8], but these scores are often complicated.

Disability. Disability is an important notion in geriatric assessment, and can include both physical and mental impairments. It is defined as the difficulty or dependency in carrying out activities essential to independent living, including both essential personal care and household tasks, and activities that are important to maintain a person’s quality of life [9]. Disability, independent of its causes, is associated with a higher risk of mortality; disabled adults are more likely to become hospitalized [10]. In patients with MM, disability can be caused by orthopaedic problems and pain; otherwise, the main causes of physical disability in the elderly are chronic diseases such as cardiovascular disease, stroke or arthritis [10].

Table 1 Levels of frailty and disability in elderly patients [9]

Frailty grade	Description
Very fit	Active, energetic patients, who exercise regularly or occasionally
Moderately fit	Patients not regularly active beyond routinely walking
Vulnerable	Patients who can perform limited activities but yet do not need help from other people
Mildly frail	Patients who need help for household tasks (shopping, walking several blocks, managing their finances, and medications)
Moderately frail	Patients who need partial help for their personal care (dressing, bathing, toileting, eating)
Severely frail	Patients completely dependent on other people for their personal care

96 *Scoring system.* It should therefore be mandatory to perform a geriatric assess-
97 ment to all elderly patients with MM, at least over the age of 70, and/or suffering
98 from any kind of frailty, comorbidities or disability. One might consider that these
99 patients should be seen and assessed by geriatricians which expertise is indis-
100 putable, but unfortunately this ideal assessment is rarely feasible due to the lack of
101 geriatricians and the increased number of elderly MM patients.

102 Very recently, a **frailty score** that combines age, comorbidities and functional
103 status (disability) has been proposed for elderly patients with MM [11]. In addition
104 to age, three tools were used: the Katz Activity of Daily Living (ADL), the Lawton
105 Instrumental Activity of Daily Living (IADL), and the Charlson Comorbidity Index
106 (CCI). In a multivariate analysis, adjusted for ISS, chromosome abnormalities and
107 type of therapy, a higher risk of death was observed for patients aged 75–80 years
108 (score = 1), and over 80 years (score = 2), and for those with an ADL score ≤ 4
109 (score = 1), an IADL ≤ 5 (score = 1) or a CCI ≥ 2 (score = 1). By combining the
110 risk scores (range, 0–5) for these variables, patients were stratified into three dis-
111 tinctive risk groups for overall survival: fit (score = 0), intermediate fitness
112 (score = 1) and frail (score ≥ 2). This frailty score could predict survival and
113 toxicity, as the “frail” group displayed an increased risk of death, progression,
114 non-hematologic adverse events and treatment discontinuation, regardless of ISS
115 stage, chromosome abnormalities and type of treatment [11]. The authors even
116 proposed an association of this frailty score with the ISS score.

117 Several questions remain unanswered; for instance, whether all patients should
118 benefit from this evaluation or only patients selected according to their age and
119 comorbidities. In routine practice, geriatric assessment is performed especially for
120 patients aged over 70–75 years and identified with comorbidities. However, if
121 geriatric assessment can help to better understand the precise geriatric risk that
122 fits each elderly patient, it could thus also be useful to identify elderly patients
123 (65–70 years, or even over 70) that could benefit from a “young” patient-based
124 therapy, if they are deemed fit enough.

125 3 Biologic and Cytogenetic Features

127 Biologic and cytogenetic features in MM are quite similar amongst the young
128 and the elderly. Most of the cytogenetic data collected in the past few years came
129 from younger, transplant-eligible newly diagnosed patients. Recently, the Inter-
130 groupe Francophone du Myélome (IFM) group reported on a series of 1890 elderly
131 patients (>65 years) [12]. Patients were classified in two groups: 66–75 years
132 ($n = 1,239$), and >75 years ($n = 651$), and incidence and clinical impact of three
133 chromosomal aberrations [del(13), t(4;14), or del(17p)] were analyzed. Interest-
134 ingly, they found a lower incidence of t(4; 14) and del(13) in the oldest patients,
135 whereas incidence of del(17p) was remarkably stable. Regardless of treatment,
136 both t(4; 14) and del(17p) were associated with a worse clinical outcome in this
137 cohort of elderly patients with MM, highlighting the importance of cytogenetic
138 analysis at diagnosis in all MM patients.



139 However, even if some data seem to suggest that VMP (melphalan-prednisone-
140 bortezomib) may overcome the adverse prognosis associated with certain high-risk
141 cytogenetic abnormalities [13], there is no certainty yet about the optimal man-
142 agement of these patients.

143 4 Response to Therapy as Primary Goal in Elderly Patients

145 The primary goal in MM has always been to improve survival across all age
146 categories, as MM remains lethal for the vast majority of patients in a median of
147 5–7 years. In elderly patients, things are not always as simple: even if prolongation
148 of disease-free survival and overall survival remains the ultimate goal, achieving
149 prolonged treatment-free intervals and good quality of life have indeed also become
150 important aims, along with avoiding complications—especially bone disease and
151 thromboembolic events.

152 A surrogate marker to survival has long been to obtain at least VGPR (very good
153 partial response). More recently, deeper responses such as CR (complete response)
154 or even MRD (minimal residual disease) have become the optimal short-term
155 endpoint, highly correlated to prolonged survival, including in elderly patients. The
156 role of CR has indeed been evaluated in a retrospective analysis of 1175 elderly
157 patients with newly diagnosed MM treated with novel agents and MP [14]. In this
158 study, achieving CR was associated with improved progression-free survival
159 (PFS) and overall survival (OS). Moreover, upon using more sensitive parameters
160 such as serum free light-chain and multiparameter flow cytometry to define the
161 depth of response, the Spanish group’s prospective analysis of elderly patients
162 receiving novel agents showed that achieving an immunophenotypic response
163 translated into better PFS compared with conventional CR or stringent CR [15].

164 However, in older patients, settling for a lower degree of response may be
165 reasonable from case to case as treatment-related toxicities could outshine any
166 benefit derived from the achievement of a CR. Despite improvement in overall
167 survival, novel agents are indeed associated with adverse events that may impair
168 quality of life (QOL) [16], which tempers down the benefit in improvement of
169 MM-related symptoms such as skeletal-related events. This impairment in QOL
170 can, however, be transient—as seen in the VISTA trial where Bortezomib was
171 associated with a deterioration of the QOL indices for the first four cycles only [17].
172 In the absence of difference in treatment efficacy, the choice of initial treatment
173 should thus be based on QOL indicators in elderly patients.

174 5 Supportive Care

176 Besides specific therapies, supportive care is essential in MM and especially in
177 elderly patients. These patients need special attention in terms of management of
178 anemia, pain (with a special focus on painkillers’ adverse effects), hypercalcemia,

179 bone disease (especially use of intravenous bisphosphonates), infections prophylaxis (crucial in elderly patients) and nutrition.

181 Occurrence of adverse events during treatment should also be carefully taken
182 into account to adjust doses and schedule.

183 **6 Review of Current Approved First-Line Therapy**
184

185 Melphalan-prednisone (MP) remained the gold standard for many years since its first
186 description by Alexanian in [18]. Combining MP with conventional agents such
187 as anthracyclines and vincristine did not improve outcome [19]; but combinations to
188 novel agents such as Thalidomide and Bortezomib finally led to an improvement in
189 overall survival. The current standards of care upfront in elderly MM patients inelig-
190 ible for autologous stem cells transplantation are thus MPT (melphalan-
191 prednisone-thalidomide) and VMP (bortezomib-melphalan-prednisone), with
192 derivatives in the alkylating agent-based backbone, with either cyclophosphamide
193 (CTD: cyclophosphamide-thalidomide-dexamethasone) [20], and bendamustine.

194 **6.1 Thalidomide-Based Therapy**

195 Thalidomide is particularly appealing in the elderly because of its lack of myelo-
196 suppression and its simple use in case of renal insufficiency, but will probably
197 become more and more outshined by the advent of novel generation drugs. Ludwig
198 et al. first showed the superiority of thalidomide-dexamethasone compared with MP
199 in elderly patients, and especially in the over 75 subgroup [21]. Hulin et al. in the
200 IFM 01/01 then reported the superiority of MPT (melphalan-prednisone-
201 thalidomide) over MP-placebo in patients older than 75 years with newly diag-
202 nosed MM [22]. A significant benefit in progression-free survival and overall
203 survival was indeed observed, and toxicity was acceptable with however more
204 grade 2–4 neuropathy and grade 3–4 neutropenia in the MPT arm. A meta-analysis
205 of published data from six randomized trials confirmed the improvement in
206 progression-free survival (PFS) and overall survival (OS) with MPT (melphalan-
207 prednisone-thalidomide) compared with MP [23]. The longer the treatment was
208 continued, the better the outcome was. The reported median PFS and OS with MPT
209 were 20.3 and 39.3 months, respectively. Toxicity, nevertheless, was always higher
210 in the MPT arm [22, 24, 25], and this regimen is likely to be dethroned by less-toxic
211 associations.

212 The combination of cyclophosphamide, thalidomide and dexamethasone
213 (CTD) also improved response rates compared with MP. Evidence from the
214 Myeloma IX trial suggested a survival benefit in CTD-treated patients with
215 favourable cytogenetics, although early deaths from infections related to high-dose
216 dexamethasone were significant [26, 27].

6.2 Bortezomib-Based Therapy

Bortezomib has excellent activity in MM at any stage of the disease and is synergistic with other agents, which led to several combination strategies.

First developed in the VISTA trial [17, 28], the addition of twice-weekly intravenous bortezomib to MP (VMP) is now a well-established regimen. VMP was proven superior to MP in response rate, CR rate, median TTP (time to progression) and OS, even over all cytogenetic and renal failure subgroups [29]. This superiority was sustained after a median follow-up of 60 months, in terms of median time to second-line antimyeloma therapy (31 months with VMP versus 20.5 months with MP) and median OS (56 months versus 43 months, respectively).

Neuropathy was the major side effect of this regimen. Changes in schedule and administration have then been made in order to reduce toxicity: the twice-weekly schedule was replaced by a weekly schedule in 2010 based on new clinical evidence [30–33] and from intravenous to subcutaneous administration in 2012 [28, 34]. Once weekly regimens are better tolerated especially in the elderly, and are associated with reduced toxicity such as neuropathy, diarrhea, constipation and thrombocytopenia [35]. Two schedules can however be discussed: a once weekly regimen from the start [31], or a twice weekly regimen for the first cycle (“VISTA” regimen) followed by a once weekly regimen for the remaining cycles [33]. It has been shown that a higher cumulative bortezomib dose, resulting from an increased dose/intensity or a prolonged treatment duration, is associated with improved OS [36]. The authors propose that dose/schedule modifications—and for instance beginning with a twice-weekly schedule, continuing therapy in responding patients, proactive management of adverse events, and subcutaneous administration of bortezomib, could help to achieve higher cumulative doses and maximize treatment duration and outcomes. The subcutaneous administration of bortezomib is indeed associated with a reduced toxicity (especially neuropathy) and similar activity [34].

Given its known efficacy and its improved safety profile, plus its easiness and in dose adaptation, VMP has now become the most prescribed regimen worldwide upfront for elderly MM.

6.3 Bendamustine Upfront in Elderly MM

The data on bendamustine are scarcer, but this drug is approved upfront with prednisone in elderly patients that could not benefit from MPT or MPV because of peripheral neuropathy. The rationale for this approval was based on a randomized trial in which bendamustine-prednisone has been proven superior to MP [37], with respect to CR rate (32 % vs. 13 %, $p = 0.007$), and with a benefit in terms of time-to-treatment failure (14 months vs. 10 months; $p = 0.020$), but without any benefit on overall survival. Bendamustine-prednisone is now an interesting option for patients ineligible for autologous stem cell transplantation, and ineligible for VMP or MPT regimens.

257 Bendamustine plus prednisone in combination with bortezomib is currently
258 being evaluated in several pilot clinical trials.

259 **6.4 Autologous Stem Cell Transplantation (ASCT)**

260 Although age does not affect the outcome of ASCT [38], the 65-year-old cut-off
261 was commonly used to determine ASCT eligibility in patients with MM for safety
262 reasons. However, the feasibility of ASCT is now well-established in fit patients up
263 to the age of 70, although it should remain a “case-per-case” decision [39]. Even if
264 evidence from the IFM 99-06 trial did not suggest any benefit of ASCT in this
265 population [24], early ASCT may nevertheless be appropriate in selected fit patients
266 between 65 and 70 years of age. Intermediate-dose melphalan (140 mg/m²) should
267 be preferred to high-dose melphalan (200 mg/m²) in this population, as retro-
268 spective data suggests a better safety profile and a similar efficacy [40]. Lower
269 doses (100–140 mg/m²) can be used for older patients.

270 Tandem ASCT with melphalan 100 mg/m² (MEL100) is another option:
271 Palumbo et al. indeed showed that tandem MEL100 ASCT was superior to con-
272 ventional MP therapy, especially in patients aged 65–70 [41]. They then reported
273 another valuable option including tandem MEL100 ASCT for elderly patients with
274 MM, especially for those aged <70: 4 cycles of bortezomib-pegylated liposomal
275 doxorubicin-dexamethasone, tandem MEL100 ASCT, 4 cycles of lenalidomide-
276 prednisone consolidation, and lenalidomide maintenance until disease progression.
277 After a median follow-up of 66 months, this sequential approach resulted in a
278 median time-to-progression of 55 months, a median PFS of 48 months, a median OS
279 not reached and 5-year OS of 63 % [42].

280 ASCT in elderly patients with significantly compromised renal function should
281 however be avoided.

282 **6.5 A New Standard of Care, Lenalidomide-Based**

283 Recently, lenalidomide plus low-dose dexamethasone (Rd) has emerged as a
284 promising new option especially in relapsed MM, or upfront in elderly patients. It is
285 an attractive option for elderly patients because of its excellent tolerability, con-
286 venience and efficacy: amongst the patients 70 and older from the ECOG study, the
287 3-year OS rate was indeed 70 % [43].

288 The IFM2007-01/MM020/FIRST study [44] compared lenalidomide-low dose
289 dexamethasone upfront in elderly MM patients, to the standard of care MPT. This
290 phase 3 multicenter trial randomized 1623 newly diagnosed elderly MM patients
291 aged 65 years or older and ineligible for ASCT, between three treatment arms:
292 melphalan-prednisone-thalidomide (MPT) administered for 12 cycles so 18 months,
293 versus lenalidomide-dexamethasone given either for 18 cycles so 18 months (Rd18)
294 or until progression or intolerance (continuous Rd). Lenalidomide was given at
295 25 mg/day for 21 days out of 28, and dexamethasone at 20 or 40 mg per week.

296 Approximately, 35 % of patients included were aged over 75 years, 47–50 % had a
297 creatinine clearance <60 mL/min and 8–10 % <30 mL/min.

298 Compared with MPT, continuous Rd significantly improved PFS, and even
299 showed an OS benefit at the interim analysis. With a median follow-up of
300 37 months, median PFS was 25.5 months for Rd, compared with 20.7 months for
301 Rd 18 and 21.2 months for MPT. Improvement in OS was significant when
302 comparing continuous Rd with MPT (estimated 4-year OS, 59.4 % vs. 51.4 %, $p = 0.0168$),
303 but not when comparing continuous Rd with Rd18 (4-year OS, 59.4 % vs. 55.7 %, $p = 0.307$). In addition, Rd was superior to MPT across all
304 other efficacy endpoints, including response rate, TTP, time to treatment failure,
305 time to second-line antimyeloma therapy and duration of response.
306

307 Moreover, median PFS and OS achieved with MPT in the FIRST study compare
308 favourably with those reported in published data: median PFS of 21.2 months
309 versus 20.3 months in the meta-analysis, and median OS of about 46 months versus
310 39.3 months, respectively [23]. Rd was thus superior to MPT intrinsically, and not
311 because MPT was less efficient than expected in this study.

312 It is worth noting that evaluation of PFS2 (PFS on second-line therapy), which is
313 now adopted as a surrogate marker for OS and was a secondary endpoint in the
314 FIRST study, also showed improvement in favour of continuous Rd as compared
315 with MPT (HR = 0.78, $p = 0.0051$).

316 Bahlis et al. recently reported that duration of response was remarkably longer in
317 patients treated with continuous Rd (35 months) versus Rd18 (22.18 months,
318 $p < 0.01$) or MPT (22.3 months, $p < 0.01$) regardless of the depth of response, but
319 the benefits of continuous Rd were even more pronounced in patients who achieved
320 a greater depth of response. When comparing continuous Rd versus Rd18 and
321 MPT, median PFS was indeed not reached versus 31 and 34.7 months, respectively,
322 for patients in VGPR, and median PFS not reached versus 45.2 and 44.6 months,
323 respectively, for patients in CR [45].

324 Concerning the safety profile, Rd was also generally better tolerated than MPT
325 [44]. Interestingly, most of the adverse events—and especially infections—were
326 mainly imputable to dexamethasone, more than to lenalidomide itself. The inci-
327 dence of thromboembolic events was slightly higher in the continuous Rd arm:
328 8 %, versus 6 % in Rd18, and 5 % in the MPT arm. Second primary malignancies
329 were higher with MPT (5 %) than with continuous Rd (3 %), which is consistent
330 with reports suggesting that the increased risk of a second primary cancer among
331 patients treated with lenalidomide may be related to prior or concurrent melphalan
332 use. Quality of life was also assessed, and was improved in all three arms of
333 treatment.

334 Lenalidomide plus low-dose dexamethasone is thus becoming a new standard of
335 care upfront for MM patients ineligible for ASCT, and has been recently approved
336 by the EMA in this indication.

337 This FIRST study has pushed the boundaries of MM treatment at least twice,
338 defining not one but 2 new changes in treatment paradigm in elderly MM patients
339 upfront: for the first time an alkylator-free option is suitable for first-line therapy,
340 and a doublet-based regimen, supposedly safer, could prove more effective than a

341 triplet-based regimen. One could foresee that some patients might never be exposed
342 to alkylators throughout their MM disease history in the near future. On the other
343 hand, one would also find of interest to compare Rd to VMP to validate the
344 superiority of Rd not only over MPT but over all MP-triplet-based regimens.
345 Indeed, the FIRST results should be interpreted with caution, as the benefit was
346 mainly observed in the continuous Rd arm once the continuous phase started (while
347 no treatment was then proposed to the other arms), and especially for responding
348 patients. Available data are insufficient for now to firmly recommend continuous Rd
349 over Rd18.

350 7 Continuous Treatment or Maintenance Therapy

352 Several studies have recently evaluated the role of continuous therapy in the form of
353 maintenance or continuous treatment for elderly MM patients upfront. These
354 approaches included:

355 7.1 Bortezomib-Based Treatments

- 356 • Bortezomib-thalidomide (VT) maintenance, following VMPT induction
357 [32, 33],
- 358 • VT or VP (bortezomib-prednisone) maintenance, following VMP or VTP
359 (bortezomib-thalidomide-prednisone) induction [30].

360 7.2 Lenalidomide-Based Treatments

- 361 • Lenalidomide maintenance after MPR (melphalan-prednisone-lenalidomide) in
362 MM015 study [46, 47],
- 363 • Continuous Rd in the FIRST study [44].

364 Taken together, these studies support the role of continuous/maintenance therapy
365 in elderly MM patients, at least in terms of PFS and time to second-line anti-myeloma
366 therapy. These survival end points indeed are almost systematically prolonged
367 by more than one year for patients exposed to maintenance versus no treatment.

- 368 • With a bortezomib-based maintenance, median PFS varies from 31 to 39 months,
369 versus 27 months without maintenance. No significant OS benefit has been pro-
370 ven for now. Amongst patients achieving CR (38–42 % of patients), results are
371 impressive, with a median PFS of 54 months and a 5-years OS of 78 % [30].
- 372 • With a lenalidomide-based maintenance, median PFS varies from 25.5 to
373 31 months, versus 13–21.2 months without maintenance, and 3-years OS is
374 estimated to be 70 % versus 62–66 % without maintenance.

375 Maintenance therapy did not manage to overcome the adverse prognosis of
376 cytogenetic abnormalities in these studies, but no increased toxicity was seen as
377 compared to standard therapy.

378 For now, lenalidomide maintenance is the only regimen that has proven safe
379 enough for long-term use, bortezomib having been studied only intravenously for
380 now. The role of subcutaneous bortezomib, novel generation proteasome inhibitors
381 particularly of oral form, or monoclonal antibodies in this setting is currently under
382 study and should pave the way for novel strategies.

383 Whether all elderly patients should receive a maintenance therapy, what type (for
384 instance monotherapy or combination), and for how long, remains an important
385 question that future studies should address.

386 **7.3 Sequential Versus Alternating Therapy, Two Keywords** 387 **in One Trial: Continuous and Switch**

- 388 • If VMP and Rd are now considered the two most effective regimens in the
389 first-line treatment of elderly MM patients, one way to further improve outcome
390 might be to find a way to combine all these drugs. However, this would
391 probably result toxic if used simultaneously. Mateos et al. recently reported
392 preliminary results for the GEM2010MAS65 trial, which compared a sequential
393 arm consisting of 9 cycles of VMP followed by 9 cycles of Rd, to an alternating
394 arm consisting on one cycle of VMP alternating with one Rd, up to 18 cycles, in
395 elderly MM patients with newly diagnosed MM [48]. These two approaches
396 were both very effective, and no difference was seen between the two arms:
397 median PFS 30 months, median OS not reached, and 3-years OS was 67 and
398 68 %. The safety profile was acceptable, although in a much lesser extent above
399 75 years old.

400 This study provided the best results ever reported in elderly patients upfront
401 compared to any other treatment approach in elderly MM; and depict what may
402 very much look like the introduction of continuous treatment in elderly MM
403 upfront. One may foresee either VMP followed by R(d) or Rd \pm X followed by
404 R(X)(d) or R(X) or X as the very likely next most used regimens for countries with
405 access to all drugs and able to prescribe continuous treatment. Nonetheless, so
406 many questions lay upon us, still.

407 **8 Future Perspectives**

408

409 Future perspectives in the treatment of elderly patients with MM include
410 improvement in treatment decision with geriatric assessment and optimization of
411 tailored therapy, favouring all-oral regimens with progress in safety profile, and
412 new families of drugs such as monoclonal antibodies.



413 **8.1 Tailored Therapy**

414 Tailored therapy in elderly patients should begin by a geriatric assessment; for
415 instance using the new frailty score recently published which includes evaluation of
416 age, disability and comorbidities [11]. The therapy decision based on frailty should
417 help us propose the optimal therapy—the safer and most efficient regimen—for
418 each category of patients with the help of specific end-points, dose adjustments and
419 toxicity management recommendations.

420 Consensual options for first-line therapy now include VMP and the newcomer
421 Rd, whereas the use of MPT should decline in the near future. It is not yet possible
422 to officially recommend one regimen over another, although several patient- and
423 disease-related characteristics may suggest one approach over the other. For
424 instance, VMP does not lead to a risk of thrombosis but instead favours neuropathy.
425 Rd is an all-oral regimen, compared to VMP that needs an hospital stay for the
426 subcutaneous administration of bortezomib.

427 An important concern is also to try and improve the survival of the poor risk
428 elderly MM patients who currently have a very short survival, and ideally overcome
429 their adverse risk profile. Indeed, while we have a clear understanding of the
430 adverse events of each therapy and thus know which patients we should avoid
431 exposure to a particular treatment, little is known about efficient tailored therapy
432 based on the risk profile, either good or poor. In the same vein, we also need to
433 propose appropriate treatments options to patients with a very good risk MM, who
434 could benefit from an intensive treatment and tend to a prolonged survival similar to
435 that of matched age-related normal individuals.

436 **8.2 Lenalidomide, a New Platform onto Which New** 437 **Regimens Are Developed, Especially** 438 **in the Elderly MM**

439 Since the FIRST study reported the impressive results obtained with
440 lenalidomide-low dose dexamethasone, a two-drug based regimen, one wondered
441 about the efficacy of a three-drug regimen using Rd as a platform. This aspect has
442 actually already been anticipated, and we should soon start to contemplate the
443 results of the first phase 3 trials with Rd used as a platform for the studied arm,
444 mostly in the context of triplet-based regimens, in the upfront setting.

445 Ongoing studies developed in this setting include:

- 446 • Rd + proteasome inhibitor bortezomib: SWOG-SO777, versus Rd
- 447 • Rd + proteasome inhibitor carfilzomib: ECOG E1A11, versus Bortezomib +Rd
- 448 • Rd + novel generation proteasome inhibitor: Tourmaline MM2: Ixazomib,
449 versus Rd
- 450 • Rd + novel class of monoclonal antibodies, elotuzumab: Eloquent 1, versus Rd
- 451 • Rd + novel class of monoclonal antibodies, daratumumab: MAIA, versus Rd.

452 Other lenalidomide-based combinations have already been studied, such as
453 lenalidomide-melphalan-prednisone (MPR), which despite a clear efficacy was
454 proven too toxic in elderly patients [46]. Dose-adjusted cyclophosphamide-
455 lenalidomide-dexamethasone (CRDa) is also under investigation by the UK group
456 (MRC-XI), with promising results in terms of early response and toxicity [49].

457 If one of these Rd-based regimens is proven effective and is approved in first-line
458 therapy for elderly MM patients, the choice of upfront therapy between Rd + X
459 compared to VMP will still have to be clarified.

460 **8.3 Monoclonal Antibodies**

461 Monoclonal antibodies finally arrived in the therapeutic arsenal of MM, even if
462 none was approved in MM so far. The recent very positive results with at least two
463 of them represent a major step forward in the management of MM. Two targets are
464 particularly promising: anti-CD38 (daratumumab and more recently SAR650984)
465 and anti-CS1/SLAMF7 (elotuzumab).

466 Great hopes are based on these antibodies, in terms of their expected ability to
467 strengthen the efficacy of current regimens and combinations, and also because they
468 are known for their very good safety profiles in the short and long term. Interest-
469 ingly, it is not expected for tumour cells to develop mechanisms of resistance to
470 these agents, which makes them even more attractive. Finally, monoclonal anti-
471 bodies will almost naturally combine to IMiDs (including thalidomide, lenalido-
472 mide and the last in line pomalidomide), the second most effective class of agents in
473 MM, whom immunomodulatory effect should reinforce significantly the action of
474 monoclonal antibodies towards tumour cells.

- 475 • CD38 is a transmembrane glycoprotein which plays a role in adhesion, sig-
476 nalling and intracellular calcium mobilization via enzymatic activity. It is
477 overexpressed on the surface of malignant plasma cells in MM, making it an
478 ideal therapeutic target. Daratumumab is a promising anti-CD38 monoclonal
479 antibody which effectively mediates destruction of CD38-expressing malignant
480 plasma cells. It was first tested as single agent in the GEN501 trial with
481 remarkable tolerance but rather modest efficacy, with an overall response rate of
482 35 % a median PFS of 23 weeks [50]. In the GEN503 trial, daratumumab was
483 tested in combination with lenalidomide and dexamethasone in relapsed or
484 refractory MM (RRMM). Tolerance was excellent and efficacy was outstanding,
485 as 75 % of patients obtained at least a very good partial response [51]. Dar-
486 atumumab was also tested in combination with various platforms (VD, VMP,
487 VTP, POM-D), which led to an overall response rate of 100 % for newly
488 diagnosed MM patients, and 50 % in relapsed MM [52]. Moreover, the addition
489 of Daratumumab was well tolerated in all evaluable patients and did not result in
490 significant additional toxicity.

- 491 • SAR650984 is another anti-CD38 antibody whose association with lenalido-
492 mide and dexamethasone allowed an overall response rate of 64.5 % in heavily
493 treated patients with RRMM, and a median PFS of 6.2 months [53]. This
494 combination was well tolerated with impressive durable responses and warrants
495 further evaluation.
- 496 • Elotuzumab is an anti-CS1/SLAMF7 antibody. The exact function of CS1 (also
497 called SLAMF7) in MM cells is not completely understood; however, previous
498 reports suggest that CS1 may be involved in cell adhesion (MM cells and bone
499 marrow stromal cells), cell cycle regulation and other growth and survival
500 pathways [54]. Targeting of SLAMF7 by elotuzumab on NK cells activate NK
501 cells. As a single agent, Elotuzumab did not show any activity in MM despite
502 plasma cell target saturation at the higher elotuzumab doses studied [55].
503 Encouraging response rates have been observed in combination with lenalido-
504 mide [56] in phase 1/2 trials, and in a much lesser extent with bortezomib [57].
505 Impressive response rate (92 %) and median PFS (not reached at a median
506 follow-up of 20.8 months) have been described with elotuzumab at 10 mg/kg in
507 combination with lenalidomide and low-dose dexamethasone in RRMM
508 patients in a phase II trial [58]. Ongoing phase 3 trials are testing elotuzumab in
509 combination with lenalidomide and low-dose dexamethasone both in the relapse
510 (Eloquent 2) and the frontline setting (Eloquent 1 and 2).

511 Monoclonal antibodies thus seem very promising agents in MM therapy, and
512 their very favourable safety profile makes them ideal candidates for elderly patients.
513 Their exact place however remains to be determined, whether they should be used
514 in addition to known regimens, and/or in consolidation or maintenance setting, as
515 an add-on or even a backbone onto which to build upon.

516 8.4 Other Drugs

517 Other proteasome inhibitors (such as carfilzomib or ixazomib), IMiDs (pomalido-
518 mide), and novel families of drugs like HDAC inhibitors (panobinostat, vorinostat)
519 or kinesin spindle inhibitors (Filanesib) are currently under investigation in the
520 relapse setting, and for some of them in the upfront setting as well already, and
521 could become valuable options in MM management in the future.

522 9 Conclusion

523
524 Management of elderly patients with MM remains challenging. The availability of
525 novel agents such as thalidomide, lenalidomide and bortezomib has improved the
526 treatment options and outcome of these patients, but has also taught us about the
527 frailty of some of these elderly patients. For the first time achievement of CR was
528 not necessarily followed by a prolonged survival, if the treatment was stopped in
529 relation to drug toxicity profile. Out of the “battlefield” that drug development looks

530 like in MM, the standards of care in first-line therapy of elderly MM patients are
531 VMP, and Rd for the very near future.

532 Other combinations, including the second and third generation of novel classes
533 and monoclonal antibodies, are under clinical development. Maintenance treatment
534 with novel agents is emerging as a new strategy to sustain disease control and delay
535 disease progression; however, the optimal maintenance regimen or molecule has yet
536 to be determined, and longer follow-up is needed to assess the optimal duration and
537 the OS benefit.

538 The optimal treatment strategy should allow a good efficacy but also a favour-
539 able safety profile, and quality of life needs to be taken into account especially in
540 elderly patients. No data are available that assess screening for vulnerability before
541 choosing and starting therapy for MM, but geriatric assessment should help to
542 develop tailored therapies for these patients in the future.

543 10 Disclosures of Potential Conflicts of Interest

545 XL and TF have received honorarium from Janssen, Celgene, Takeda, Amgen,
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