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SPECIAL PROBLEMS IN THE MANAGEMENT OF ELDERLY PATIENTS WITH MULTIPLE MYELOMA

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ABSTRACT

Multiple myeloma (MM) is a neoplastic disease typical of the elderly. Many steps forward have been made both for the characterization of patients and new treatment strategies are available today. Clinical trials represent a major point in the definition of standard treatment, nevertheless, fit patients are enrolled, while frail patients are commonly excluded. Therefore, frail patients may receive treatments that may be too toxic and thus jeopardizing the beneficial effects of therapy. A careful patient assessment is crucial to better characterize patients and consequently to appropriately select treatment. Future trials testing novel agent-based therapies in different subsets of patients will shed light on this important issue and will allow patients to receive appropriate, tailored treatments.

INTRODUCTION

Multiple myeloma (MM) is a neoplastic disease deriving from an abnormal proliferation of monoclonal plasma cells in the bone marrow. MM is characterized both by intrinsic genetic alterations in the clonal plasma cells and by micro-environmental changes.[1]

The diagnosis of MM requires the presence of at least 10% of monoclonal plasma cells in the bone marrow. Symptomatic myeloma is defined by the presence of organ damage (the so-called CRAB symptoms: C: hypercalcemia [> 11.5 mg/dL]; R: renal failure [serum creatinine > 1.73 mmol/L]; A: anemia [hemoglobin < 10 g/dL or > 2 g/dL below the lower limit of normal]; and B: bone disease [lytic lesions, severe osteopenia or pathologic fractures]) and requires prompt treatment.[2] Recently, the diagnostic criteria have been re-defined with the inclusion of new clinically relevant criteria, named as MM defining events, whose presence is an indication to start treatment: more than 60% of monoclonal plasma cells in the bone marrow, more than one focal lesions identified with magnetic resonance imaging (MRI), or a serum free-light chains (FLC) ratio >100 with the involved FLC > 100 mg/dL.[3]

The incidence of MM grows markedly with age: ~70% of patients are older than 65 years and ~40% are older than 75 years.[4] Considering the worldwide population, elderly people older than 80 years are expected to increase from currently 3 million to 6 million by 2030. As a consequence, the overall incidence of MM diagnoses will further grow, inducing the necessity of new treatment options and appropriate strategies for elderly patients.

Many steps forward have been made in the treatment of MM: thalidomide, bortezomib, and lenalidomide strongly contributed in recent years to improve the median progression-free survival (PFS) and overall survival (OS), the latter being increased by about 4 years in newly diagnosed MM patients (NDMM) since 2000.[5] Of interest, a significant improvement in OS was seen also among patients older than 65 years, where the 6-year OS improved from 31% to 56% ($P<0.001$).[6] This is likely related to the increased use of the newer drugs also among older patients and to a decrease

in early mortality, which reflects a better management of treatment related toxicities, due to improved supportive care and to the adoption of an “age-adjusted” treatment approach[7].

Nevertheless, advanced age (over 70, but especially over 80 years) is still one of the factors predicting early mortality, reflecting the impact of comorbidities and geriatric impairments on outcome. Both comorbidities and geriatric impairments can in fact increase the risk of treatment-related toxicities and, as a consequence, decrease the ability to effectively administer treatment.

Elderly patients are a highly heterogeneous population, with different levels of vulnerability; in such population, well-known biologic and genetic prognostic disease-related factors, as well as age per se, are insufficient to explain different disease and treatment outcome.

The aim of this review is to better characterize older MM patients, based on current available data, thereby defining the appropriate treatment.

Frailty status and geriatric assessment

Elderly patients are psycho-socially and physically heterogeneous and chronological and biological age often do not coincide. Patients’ allocation in randomized studies does not properly take into account ageing and frailty. Nevertheless, as the incidence of MM is higher in older people, this patient subset certainly needs particular attention: comorbidities, disability, and frailty need to be assessed, and appropriate sensitive tools are needed.

MM patients $\geq$75 years treated upfront with newer agents may have similar PFS as younger patients, although their OS is impaired. This is likely due to the fact that adverse events from first-line therapies may preclude second-line therapies, and third-line therapies in >80-year old MM patients are quite uncommon. Elderly patients are often affected by progressive decrease in physiological reserve, changes in body composition and clinically-impacting reductions in renal function, gastric function, hepatic mass and blood flow, bone marrow status, and cardiovascular function.[8–11] In addition, they are more vulnerable to side effects and frequently present comorbidities, which may likely lead to adverse events and early discontinuation. Therefore, it is important to identify dedicated strategies for specific subgroups of patients, in order to improve safety and efficacy of first-line and subsequent treatments [12].

Since few years ago, MM patients were commonly defined frail if older than 75 years, and they were consequently undertreated merely based on age. Recently, different scores and indexes have been introduced in the MM setting, including a more complete geriatric evaluation. The geriatric assessment (GA), commonly used by geriatricians and oncologist in the treatment decision process, is an objective frailty predictor, which categorizes patients focusing on somatic, functional and psychosocial domains.[13] In 2015, the International Myeloma Working Group (IMWG) developed a frailty score including age, functional status and comorbidities, in order to determine the frailty status of patients and the feasibility of different treatments. Based on a pooled analysis of 869 newly diagnosed elderly patients enrolled in 3 prospective trials an additive scoring system (range 0-5) was

developed to detect and define frailty based on age, Charlson Comorbidity Index [CCI], Activities of Daily Living [ADL] and Instrumental Activities of Daily Living [IADL] (Figure 1). According to this score, 3 groups of patients were identified: fit (score=0, 39%); intermediate (score=1, 31%), and frail patients (score≥2, 30%).[14] The frailty score predicted mortality and PFS in elderly patients and demonstrated that the prognostic impact on OS was independent from ISS, chromosomal abnormalities, type of treatment and performance status in multivariate analysis. Of note, grade ≥3 non-hematologic AEs and treatment discontinuations due to toxicity were also higher in frail patients. This frailty score calculator is available online (http://195.88.6.191/Frailtyscore/). A validation of the IMWG geriatric scale in an independent series of NDMM patients confirmed the score's impact on outcome.[15]

Recently, renal, lung, performance status impairment, frailty and age were combined in a weighted revised Myeloma Comorbidity Index, allowing for the identification of fit (Index ≤3), intermediate (Index 4–6) and frail patients (>6); these subgroups showed median OS rates of 10.1, 4.4 and 1.2 years, respectively. The Myeloma Comorbidity Index proved to be another useful instrument to identify the geriatric risk profile of MM patients and have a prognostic value for functional decline and OS.[16]

Other biomarkers such as sarcopenia (the decreased skeletal muscle mass) which predicts outcomes in patients with solid tumors,[17] and N-terminal natriuretic peptide type B (NT-proBNP),[18] are under evaluation.

The therapeutic shift represented by newer agents with a better safety profile did not diminish the challenge of choosing the proper therapy for elderly MM patients: the “one size fits all” approach is clearly no longer a sensible option and patients should be appropriately evaluated to determine their ability to tolerate treatment.

Treatment adherence and compliance

Frailty, comorbidities, decrease organ function, are all factors that make patients more vulnerable to side effects, which may likely lead to severe adverse events and early discontinuation.[8–11] This inevitably impacts on treatment adherence and may compromise treatment efficacy. Indeed, a large meta-analysis (1435 elderly patients enrolled in 4 randomized trials and treated with thalidomide and/or bortezomib) demonstrated that the risk of death was higher in patients aged 75 years or over (HR 1.44, 95% CI 1.20-1.72; P<0.001), in patients with renal failure (HR 2.02, 95% CI 1.51-2.70; P<0.001), in those who developed grade 3-4 infections or cardiac/gastrointestinal adverse events during treatment (HR 2.53, 95% CI 1.75-3.64; P<0.001), and in those who required drug discontinuation due to adverse events (HR 1.67, 95% CI 1.12-2.51; P=0.01). Most noteworthy, the estimated 3-year OS was 68% in patients ≤75 years and 57% in those ≥75 years (HR 1.44, 95% CI 1.20-1.72; P<0.001).[19]

The other foremost intricacy in the treatment of elderly MM patients is the compliance with the treatment itself. Both physical and mental limitations can entail disability, which is defined as a difficulty or dependency in performing activities essential to independent living, including both personal care and domestic tasks, and activities that are important to preserve the quality of life[20–22]. Frail patients affected by mental or cognitive impairments may present serious issues in terms of compliance with oral treatment and require the supervision of a care-giver - as oral drugs are meant to be taken at home without medical supervision. On the other hand, intravenous or subcutaneous strategies often require hospital visits, thus representing a potential limitation to elderly patients with mobility impairment, pre-existing disability, and/or lacking caregiver support and training. Bone lesions due to MM itself may further affect patients' inability to attend hospital visits. Therefore, a proper evaluation of patients and a careful selection of therapy are required in the elderly frail population, in order to solve difficulties related to both treatment adherence and treatment compliance.

Treatment strategies in newly diagnosed elderly MM patients

In Europe, the triplet bortezomib-melphalan-prednisone (VMP) is one of the standard treatments for elderly patients. In the VISTA study, VMP proved to be superior to the former standard, melphalan-prednisone (MP), in terms of PFS (median: 24 vs. 16.6 months, respectively; HR 0.48; P<0.001) and OS (median OS: 56.4 vs. 43.1 months, HR, 0.695; P<0.001).[23,24] The survival benefit with VMP was detected in the different pre-specified patient subgroups defined by age (≥75 years), disease stage (stage III), renal function (creatinine clearance <60mL/min). Peripheral neuropathy (PNP) is the major concern when using bortezomib; nevertheless, its incidence can be considerably reduced, without affecting efficacy, by adopting once-weekly rather than twice-weekly dosing,[25] subcutaneous rather than intravenous route, and strict dose reductions in the case of grade 3-4 toxicities.[26])

A more intense approach was tested in the GIMEMA-MM-03-05 trial, which compared VMP-thalidomide followed by 2 years VT maintenance (VMPT-VT) to the standard VMP.[27,28] After a median follow-up of 54 months, the median PFS was considerably better with VMPT-VT than with VMP (35.3 *vs* 24.8 months, respectively; HR, 0.58; P<0.001) and the 5-year OS was also improved (61% vs. 51%; HR, 0.70; P <0.01).

The PETHEMA group evaluated and alkylating-free regimen bortezomib-prednisone-thalidomide (VPT) compared with VMP.[29,30] After induction, patients were randomized to maintenance with bortezomib-thalidomide (VT) or bortezomib-prednisone (VP). The median PFS was 32 months for the VMP and 23 months for the VTP arms (p=0.09). VMP significantly prolonged OS compared with VTP (median of 63 and 43 months, respectively; HR: 0.67, p=0.01).[30] From the beginning of maintenance, PFS was 32 months for patients receiving VT *vs* 24 months for those receiving VP (HR 1.4, 95% CI 0.8–2.1; p=0.1), with no difference in OS (HR 1.2, 0.6–2.4). Nevertheless, the

incidence of adverse events, especially arrhythmia and cardiac events, was higher with VT than VP. [29,30]

The phase III CLARION trial evaluated an alternative regimen, comparing carfilzomib-melphalan-prednisone (KMP) *vs* standard VMP for a fixed duration of 9 cycles.[31] This study did not find any statistically substantial difference in PFS (22.3 months with KMP *vs* 22.1 months with VMP; HR, 0.91; 95% CI, 0.75–1.10). Median OS was not reached in either group (HR 1.08, 95% CI 0.82-1.43). In Europe, based on the aforementioned data, VMP is currently the only proteasome inhibitor-based approved standard for elderly patients with newly diagnosed MM.

More recently, an immunomodulatory drug-based induction has been approved as a standard approach for elderly patients, namely the doublet lenalidomide-dexamethasone (Rd). This combination was evaluated in the FIRST trial, which demonstrated that continuous treatment with Rd significantly improved PFS compared to MPT.[32] Indeed, continuous Rd substantially decreased the risk of disease progression compared to MPT (HR 0.72; p=0.0006) and Rd 18 (HR 0.70; p=0.0001), whereas no relevant PFS difference between Rd 18 and MPT was found (HR 1.03; p=0.7035). Median PFS with continuous Rd, Rd 18 and MPT was 26, 21 and 21.9 months, respectively. The PFS benefit of continuous Rd was detected in various subgroups, including age, ISS stage, renal function, performance status, but not in high-risk patients defined by the presence of increased lactate dehydrogenase (LDH) or high-risk cytogenetics. Rd significantly improved also OS compared to MPT; no OS differences were instead noticed between continuous Rd and Rd18. [32] Interestingly, continuous Rd treatment showed better clinically relevant health-related-quality-of-life measurements (HRQoL) over the course of treatment, and better QoL-related to treatment side effects as compared to MPT.[33] Therefore, the old standard MPT is no longer considered a first option.

A direct comparison between VMP and Rd regimens is yet to be done. Nevertheless, the Spanish group evaluated both VMP and Rd regimens adopted in different sequences: a sequential scheme with 9 cycles of VMP followed by 9 cycles of Rd *vs* one cycle of VMP directly followed by Rd in an alternate fashion for up to 18 cycles.[34] Similar median PFS (32 *vs* 34 months, p=0.65) and 3-year OS (72% vs. 74%, respectively; p=0.63) were detected; hematologic and non-hematologic toxicities were analogous with the two approaches. Because no trial directly compared VMP *vs* Rd, the alleged superiority of one regimen over the other needs to be properly demonstrated (Table 1).

Beyond approved standard therapies in Europe, other alternatives have also been investigated. The Southwest Oncology Group (SWOG) and the National Clinical Trial Network (NCTN) performed a phase 3 study to compare intravenous bortezomib-lenalidomide-dexamethasone (VRd) *vs* standard Rd in NDMM patients, stratified according to the intent to transplant or not.[35] Although VRd showed higher PFS (43 vs. 30 months, respectively; HR 0.712, 96% CI 0.56-0.906; p=0.0018) and also better OS (75 vs. 64 months, respectively, HR 0.709, 95% CI 0.524-0.959; p=0.025) with acceptable toxicity, no ultimate conclusions about the treatment of elderly MM patients can be derived, since

this study was not restricted to elderly patients ineligible for transplant. However, VRd surely remains a valid option for fit elderly patients. Based on these results, VRD regimen is now approved in the USA for the upfront treatment of MM patients.

Treatment selection

Treatment selection is undoubtedly challenging when it comes to elderly patients. Many factors need to be sensibly considered, and the optimal strategy should balance efficacy and toxicity, especially in frail patients. The available therapies already approved in Europe have been mostly tested in selected fit patients eligible for clinical trials, and may not be appropriate for frail elderly patients who may not tolerate standard regimens, with high rates of toxicities and treatment discontinuation.

Therefore, a geriatric assessment may help to identify frail patients, and modulate treatment objectives based on frailty status. Fit patients can be treated with full-dose therapies. For very fit patients up to the age of 70 with no comorbidities, even transplant could be considered an option, provided that a complete work-up does not show any comorbidities or organ impairment. As alternative, full-dose standard regimens (VMP or Rd, VRd or VMP/Rd if approved) are all valuable options. Intermediate fit patients need less intensive regimens or doublet regimens, and frail patients may benefit from dose-reduced doublet therapies or even a more palliative approach (Figure2). Consistently, the goal of therapy is different in these 3 groups: the goal of therapy for fit patients is to achieve a complete remission and improve survival, as in younger and fit patients; for intermediate fit or frail patients, for whom comorbidities and treatment toxicities hamper efficacy of full-dose therapy, the main objective of therapy is to improve and preserve the quality of life as long as possible.

Because randomized trials comparing the two European Standards (VMP and Rd) are lacking, treatment choice should be based on patient characteristics, patient preference and compliance. Data from subgroup analyses suggest that, whenever there is no contraindication to one of the two treatments, patients with high-risk disease may benefit of proteasome inhibitor-based treatment, and immunomodulatory drug alone could be suboptimal. The efficacy and safety profile of bortezomib favors the use of this drug also in patients with renal failure; lenalidomide is an option, after appropriate dose reductions. Oral administration, and long-term tolerability (absence of peripheral neuropathy), on the other hand, are undoubtedly advantages in the treatment of elderly patients.

Management of toxicities

In elderly patients, early detection of toxicities, prompt treatment interruption (if needed), management of treatment-related side effects with applicable supportive care are fundamental. Supportive care is essential to preserve a proper quality of life and to help patients to stay on treatment. A precise account of the patient's previous medications and an appropriate awareness of potential drug interactions are essential before starting therapy.[36]

Cytopenia is frequent in hematologic patients treated with chemotherapy. It involves one or more cellular lineages of the bone marrow, and can be induced by neoplastic cells invading the bone marrow or by chemo-toxicity. [37,38]

Anemia is characterized by a hemoglobin level <13.5 g/dL for men and <12.0 g/dL for women. In elderly patients, anemia may be caused by plasma cells proliferation or chemotoxicity, but also by renal insufficiency, iron, and vitamin deficiency (folic acid, B12 vitamin), hypogonadism, relative erythropoietin system impairment, underlying myelodysplasia, or exhaustion of the hematopoietic progenitor. Approximately 50% of patients with anemia have two or more interrelated causes. It is therefore important to investigate and treat all possible concomitant causes of anemia. Blood transfusions are recommended with hemoglobin levels <7-8 g/dl. Erythropoietin-stimulating agents can soothe fatigue and improve quality of life, allowing treatment to be continued.[39]

Patients affected by neutropenia after chemotherapy are also at risk of infections. When neutropenia occurs (less than 1000/mmc in frail/unfit patients or less than 500/mmc in fit patients), especially if prolonged, a prompt antibacterial prophylaxis together with Granulocyte Colony Stimulating Factor (G-CSF) administration, can prevent febrile episodes, clinically or microbiologically documented bacterial infections (including bacteremias), and hospitalization of outpatients.[40] In case of short-term neutropenia, in particular in fit patients, the benefit of anti-biotic prophylaxis should be carefully evaluated together with the risk of development of antibiotic resistance. Prophylaxis with antifungal agents (usually azoles) is encouraged in case of prolonged neutropenia. All patients treated with chemotherapy or novel agents-based therapy should be administered trimetophrim-cotrimoxazole as a prophylactic agent against the opportunistic infection of Pneumocystis Jirovecii pneumonia.

Febrile neutropenia is defined by an oral temperature >38.5°C or by two consecutive measurements with a temperature >38.0° C for 2 hours, and by an absolute neutrophil count of less than 0.5 x 10^9/L or one expected to fall below 0.5 x 10^9/L. Chemotherapy-induced febrile neutropenia is a major risk factor for infection-related morbidity and death, as well as a significant dose-limiting toxicity. Prognosis is worst in patients with bacteraemia, with mortality rates of 18% in Gram-negative and 5% in Gram-positive bacteraemia.[41] Prophylactic G-CSF should be administered to elderly patients at high risk of developing febrile neutropenia, taking into account their age, medical history, disease characteristics, and the myelotoxicity of their chemotherapy regimen. In patients with febrile neutropenia, the choice of initial antibiotic should be based on patient's infectious disease history, prior antibiotic usage, and epidemiologic data of the area where the patient lives.

In patients receiving proteasome inhibitors, antiviral prophylaxis for Herpes Zoster reactivation is necessary.

Immunomodulatory agents require a proper risk-based thromboprophylaxis.[42,43] Risk factors for thrombosis include uncontrolled disease and reduced mobility, two factors often preset at the time of diagnosis or relapse, and in patients with bone disease. In these cases, LMWH is the option of choice.

When corticosteroids are administered, gastrointestinal prophylaxis should be adopted. Long-term lenalidomide therapy may be associated with recurrent diarrhea, and colestiramine treatment can be helpful in controlling the symptoms.

Peripheral neuropathy is an issue with the use of bortezomib. Prompt dose reductions are needed in case of grade 1 with pain or grade 2, and dose should be reduced to 1.0 mg/m2; for grade 2 with pain or grade 3 peripheral neuropathy, treatment interruption is indicated until resolution to at least grade 1 with re-initiation at 0.7 mg/m2/week; for grade 4 peripheral neuropathy, treatment should be discontinued. Alternatively, if grade 1 with pain occurs, the biweekly bortezomib infusion can be reduced to weekly infusion; if grade 2 or higher occurs, bortezomib should be stopped until resolution to grade 1, and then it can be restarted on a weekly basis.[38]

In case of adverse events during treatment, dose reductions represent a valid strategy to allow patients to continue therapy. Therapy should be stopped in case of grade 3-4 toxicity, and may be restarted at lower doses when toxicity decreases to at least grade 1. The dose of lenalidomide may be decreased from 15 to 10 mg/day, or from 10 to 5 mg/day or, if required, to 5 mg every other day on days 1-21 every 4 weeks. Bortezomib may be reduced from 1.3 mg/m^2 once weekly to 1.0 mg/m^2 once weekly or 0.7 mg/m^2 once weekly.

CONCLUSIONS

Elderly patients represent the majority of MM population, thus they clearly need particular consideration. First, an appropriate assessment of their frailty status is essential to guide clinicians in selection of the most suitable treatment. In this light, the use of a standardized minimum dataset of tools and biomarkers to define frailty of MM patients will permit comparison of results between different studies. More efficient methods to detect and grade the severity of frailty as part of routine clinical practice are needed, as well as clinical trials specifically designed for tailored treatment according to frailty status. Indeed, frail patients may not benefit from standard and full-dose regimens commonly used in fit patients, and alternative, gentler approaches should be adopted.

Elderly patients are also more easily susceptible to adverse events, often leading to treatment interruption and poor quality of life. This is particularly evident in frail patients. Therefore, dose adjustments at the beginning of treatment, as well as prompt action and dose reduction at the occurrence of any toxicity, are fundamental. These strategies can in fact help patients to continue their assigned treatment and benefit from it.

To date, clinical trials have assessed approaches in selected fit patients, and future prospective trials need to investigate different tailored therapies in frail MM patients.

Second generation agents are currently being assessed, and new effective and safe combinations are likely to enter the treatment armamentarium against MM soon. Of note, monoclonal antibodies have revolutionized treatment of myeloma, and the low toxicity is certainly a major advantage,

particularly in the setting of elderly frail patients. Therefore, future trials testing these new agents in different subsets of patients are urgently awaited.

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Table 1. Selected induction therapy for elderly MM patients

Study	G3-4 Neut	G3-4 GI	G3-4 PN	ORR	CR	Median PFS (mo)	Median OS (mo)
VMP (VISTA)[23,24]	**40%**	**19%**	**13%**	**71%**	**30%**	**21**	**56**
Rd continuous (FIRST)[32]	**28%**	**2%**	**1%**	**75%**	**15%**	**26**	**59**
VRD (SWOG)*[35]	**NA**	**52%**	**33%**	**81%**	**16%**	**43**	**75**
VMP/Rd (PETHEMA)[34]	**19-22%**	**6%**	**4%**	**76%**	**25%**	**32**	**64**

** The study included both younger and elderly patients (patients ≥65 years: 43%)*

VMP, bortezomib-melphalan-prednisone; Rd,lenalidomide-dexamethasone; VRD, bortezomib-lenalidomide-dexamethasone; G, grade; Neut, neutropenia; GI, gastrointestinal; PN, peripheral neuropathy; ORR, overall response rate; CR, complete response; PFS, progression-free survival; OS, overall survival; mo, months.

Figure 1. MM Frailty Score

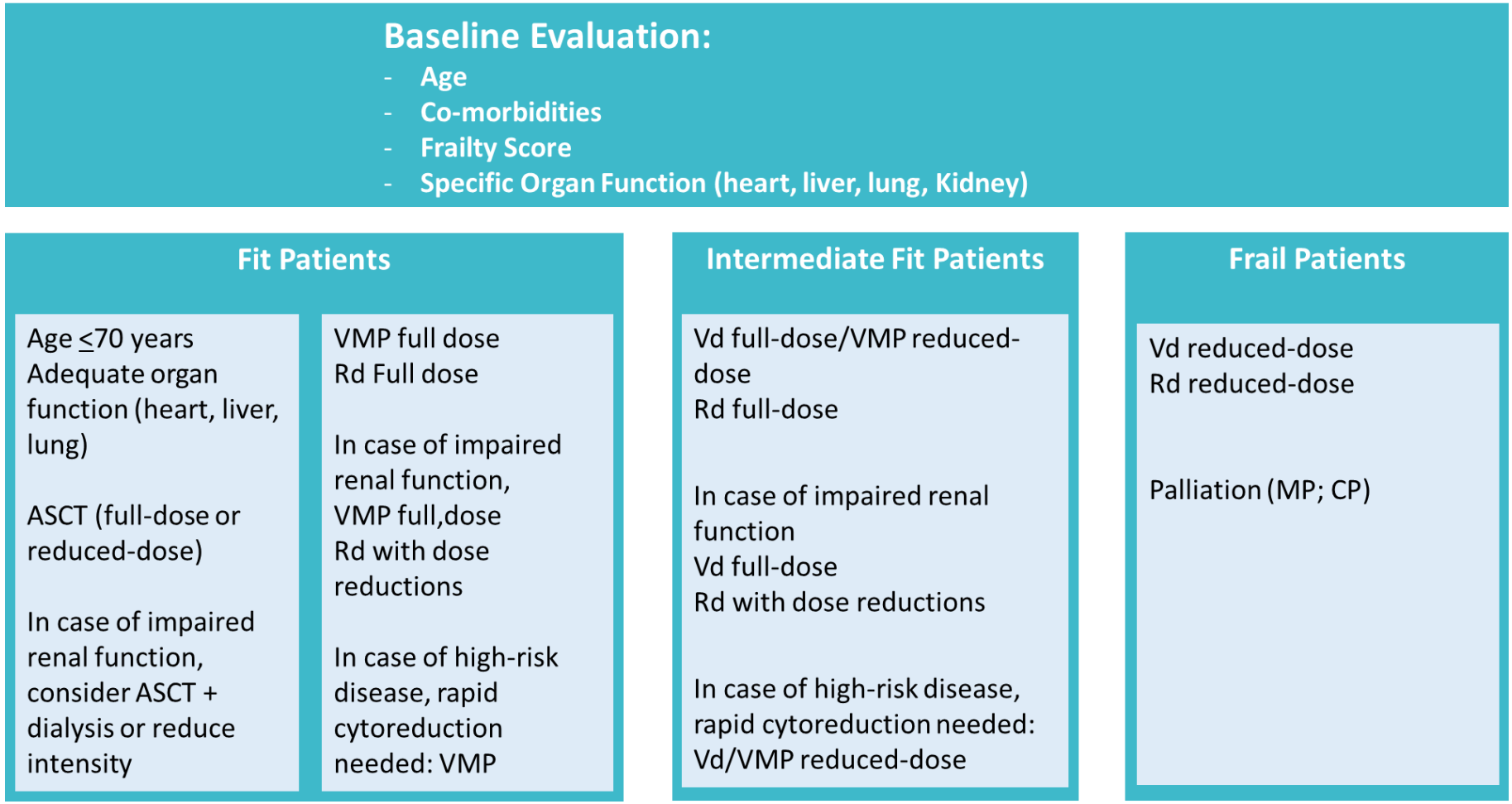
Variable		HR (CI 95%)	P	SCORE
AGE	Age <75 years	1	-	0
	Age 75-80 years	1.13 (0.76-1.69)	0.549	1
	Age >80 years	2.40 (1.56-3.71)	<0.001	2
CHARLSON INDEX	Charlson ≤1	1	-	0
	Charlson ≥2	1.37 (0.92-2.05)	0.125	1
ADL SCORE	ADL >4	1	-	0
	ADL≤4	1.67 (1.08-2.56)	0.02	1
IADL SCORE	IADL >5	1	-	0
	IADL≤5	1.43 (0.96-2.14)	0.078	1

ADDITIVE TOTAL SCORE	PATIENT STATUS
0	**FIT**
1	**INTERMEDIATE**
≥2	**FRAIL**

ADL, activity of daily living; IADL, instrumental activity of daily living; HR, hazard ratio

Palumbo A et al, Blood 25(13):2068-74, 2015. Available online http://195.88.6.191/Frailtyscore/

Figure 2. Suggested treatment options according to frailty status



ASCT, autologous stem cell transplantation; VMP, bortezomib-melphalan-prednisone; Rd, lenalidomide-dexamethasone; Vd, bortezomib-dexamethasone; MP, melphalan-prednisone; CP, cyclophosphamide-prednisone.