Latest advances in the management of elderly patients with multiple myeloma

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In the last few years many advances have been made in the understanding and treatment of multiple myeloma (MM). MM is a plasma cell neoplasm that accounts for approximately 10% of all hematologic malignancies, it is typical of the elderly, with a median age at diagnosis of 65 years [101].

The diagnosis of MM requires the presence of at least 10% clonal plasma cells on bone marrow examination and/or a biopsy-proven plasmacytoma, as well as evidence of end-organ damage, the so-called ‘CRAB’ symptoms (hypercalcemia, renal insufficiency, anemia or bone lesions) [1]. Although there has been recent discussion about time of treatment, so far no benefit from starting therapy earlier has been evidenced, and thus treatment should be given only when end-organ damage occurs [2].

Patient’s age commonly plays an important role when choosing therapy. The age of 65 years is considered the cutoff for whether a patient is eligible for high-dose therapy followed by autologous stem cell transplantation (ASCT). For patients younger than 65 years and with

no comorbidities, high-dose therapy and ASCT can be adopted, while for patients older than 65 years, as well as for patients younger than 65 years but with comorbidities, a gentler approach not including ASCT is preferred [2]. However, this strict age cutoff should be considered with caution, since chronological age does not always correspond to biological age. Owing to the increased life expectancy of the general population, the incidence of cancer, including MM, is also rising and physicians have to come to terms with an increasingly heterogeneous patient population. This has inevitably presented new challenges in the therapeutic approach for MM, particularly for older patients.

Indeed, aging is associated with reduced organ function and consequently a higher susceptibility to treatment-related adverse events [3]. Therefore, a careful geriatric assessment is suggested and different recently available geriatric scores may be used to appropriately evaluate patients [3,4]. Based on such scores, patients can be classified as very fit, fit and unfit. Unfit patients are characterized by older age, comorbidity, organ dysfunctions

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(e.g., cardiac, pulmonary, hepatic, gastrointestinal and renal) and limits in mental/mobility functions. For these patients, reduced-intensity approaches are needed, while full-dose therapy can be adopted for fit patients.

The International Staging System (ISS) is commonly used to assess the prognosis of patients with MM, with ISS stage III being associated with a poor prognosis [5]. Similarly, chromosomal abnormalities t(4;14), t(14;16), t(14;20), chromosome 1 abnormalities, and del17p detected by FISH are associated with poor prognosis [6]. Recently, combining both ISS and FISH data has improved the risk assessment of MM patients. More sophisticated techniques, such as gene-expression profiling, are being tested and used to stratify patients and to predict their prognosis [7]. The prognostic role of PET/computed tomography is under investigation but it needs to be validated before it is adopted into standard practice [8]. In addition, several studies demonstrated that patients who achieve a complete response after initial treatment have an improved progression-free survival (PFS) and overall survival (OS) [9].

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The treatment paradigm of MM has been particularly revolutionized by the introduction of the immunomodulatory drugs thalidomide and lenalidomide, and the proteasome inhibitor bortezomib. These agents enabled physicians to provide MM patients with more appropriate and tailored approaches, with considerable improvements in survival also seen in elderly patients [2].

In very fit elderly MM patients, that is with excellent clinical condition and biological age younger than actual chronological age (very good cardiac, pulmonary, hepatic, gastrointestinal and renal functions), reduced-intensity ASCT with melphalan 100 mg/m² (MEL100) can be safely used. In a Phase II trial, bortezomib-based induction, tandem MEL100, lenalidomide–prednisone consolidation, and lenalidomide maintenance led to a median PFS of approximately 4 years [10].

In fit elderly MM patients, namely those with good clinical conditions but not eligible for ASCT, full-dose novel-agent-containing combinations should be used. In a meta-analysis

including data from six randomized Phase III studies, thalidomide plus melphalan–prednisone (MPT) prolonged PFS by 5.4 months and OS by 6.6 months compared with the older standard melphalan–prednisone regimen alone [11]. In a randomized Phase III study, bortezomib plus melphalan–prednisone (VMP) also showed improved complete response rate (30 vs 4%), time-to-progression (23 months vs 16 months) and OS (56 months vs 43 months) as compared with melphalan–prednisone [12]. Both MPT and VMP are now considered the new standards of care in Europe.

Alternatively, although not supported by a randomized Phase III study, the combination bortezomib–lenalidomide–dexamethasone (VRD) is used, particularly in the USA. VRD induced a complete response/near complete response rate of 39% and an 18-month PFS rate of 75% [13]. In a Phase III trial, VRD was compared with bortezomib–cyclophosphamide–dexamethasone (VCD) and bortezomib–cyclophosphamide–dexamethasone–lenalidomide. In this trial, both VRD and VCD were shown to be effective with at least a very good partial response rate of 51 and 53%, and 1-year PFS of 83 and 100%, respectively [14].

The role of consolidation/maintenance therapy with novel agents has been confirmed in different studies. Lenalidomide maintenance seems to be a sensible strategy. In a Phase III study, melphalan–prednisone–lenalidomide (MPR) followed by lenalidomide (MPR-R) induced higher complete response rate (10 vs 3%) and longer PFS (31 months vs 13–14 months) compared with MPR and melphalan–prednisone [15]. Bortezomib plus thalidomide maintenance is another possible alternative. A Phase III study showed that bortezomib–melphalan–prednisone–thalidomide followed by bortezomib–thalidomide (VMPT-VT) improved the complete response rate (38 vs 24%) and the 5-year OS (59 vs 45%) compared with the standard VMP [16]. Despite these results, MPR-R and VMPT-VT are quite intensive regimens for patients over 75 years of age, and are thus more suitable for patients aged under 75 years.

Conversely, unfit patients apparently benefit more from gentler approaches that induce lower toxicity and enable them to stay on therapy longer. In these patients, reducing the drug doses of standard MPT or VMP seems a sensible strategy to achieve this aim [2]. Alternatively, two-drug regimens should be selected. Indeed, a Phase III

study showed that bortezomib–dexamethasone was associated with a lower complete response rate (30%) compared with bortezomib–thalidomide–dexamethasone (40%) and VMP (33%), but induced less toxicity and discontinuations [17]. Lenalidomide plus low-dose dexamethasone is a valid alternative and should be preferred to lenalidomide plus high-dose dexamethasone because of the OS advantage (at 2 years: 87 vs 75%), particularly in patients older than 65 years [18]. Starting with a two-drug regimen and, if tolerated, intensifying by adding a third agent can be a valuable approach in unfit patients. This has been tested in a Phase II study, where patients were first given lenalidomide–prednisone induction; subsequently, melphalan was added (MPR) and finally lenalidomide–prednisone maintenance was administered [19].

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Based on these considerations, it is clear that age can no longer be the only prognostic factor to consider when selecting therapy. In fact, many differences exist even within the same age group.

A careful geriatric assessment, as well as an adequate and more refined prognostic evaluation, can help physicians choose the most appropriate treatment. Future studies will confirm the role of new prognostic factors, and tailored effective therapies should be provided to improve quality of life of the patients and avoid improper use of resources. Moreover, newer novel agents such as new oral proteasome inhibitors, new-generation immunomodulatory drugs, monoclonal antibodies and histone deacetylase inhibitors are under investigation and they will increase the treatment plethora for these patients.

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