Multiple myeloma treatment in the elderly

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“...there is ample clinical evidence to argue against a fatalistic approach in elderly multiple myeloma patients.”

The outcome of multiple myeloma (MM) has significantly improved during recent decades. While chemotherapy and steroids have been the backbone of myeloma treatment for years, the immunomodulatory drugs thalidomide and lenalidomide, and the proteasome inhibitor bortezomib (these three drugs are frequently referred to as ‘novel agents’) have dramatically changed the treatment paradigm and improved the prognosis of the majority of MM patients. Based on *in vitro* data and supported by many clinical trials, there is ample proof that these novel agents can be successfully and safely combined with more conventional drugs such as chemotherapy and steroids, creating several possible treatment regimens with potent antimyeloma activity. Importantly, a rational combination and/or sequential approach of these antimyeloma drugs can significantly prolong progression-free survival (PFS) and even overall survival (OS). Nonetheless, MM remains an incurable disease for the majority of patients. Optimization of front-line treatment is a necessary prerequisite to maximize long-term outcome in MM. In that regard, one should keep in mind that MM is primarily a disease of the elderly

patient, with a median age of 70 years at diagnosis. For one third of patients referred to as the younger age cohort (<65 years), treatment recommendations at diagnosis are relatively uniform consisting of a novel-agent based induction regimen, one or two autografts, eventually followed by consolidation and/or maintenance treatment [1,2]. With this approach, high rates of complete remissions can be achieved, generally accepted as one of the strongest predictors for a prolonged treatment-free interval and improved OS [3]. Variations in treatment approach in the younger age cohort do occur, but they are mostly driven by disease characteristics such as cytogenetics, and more exceptionally by patient-related comorbidities. By contrast, elderly MM patients rarely qualify for high-dose chemotherapy, and because of concomitant diseases and disabilities their front-line treatment is more heterogeneous. An important question one should ask at treatment initiation is about the ultimate treatment goal. Does one aim for the highest level of response at the expense of side effects, or for disease control with a more gentle therapeutic approach. As will be discussed here, both strategies are not

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necessarily contradictory. With the current anti-myeloma regimens even allowing some degree of therapeutic individualization, high levels of response can be achieved with manageable side effects [4].

Until a decade ago, melphalan plus prednisone (MP) was the standard of care for newly diagnosed elderly MM patients. Not surprisingly, an outcome analysis of the Surveillance, Epidemiology, and End Results (SEER) program between 1992 and 2004 failed to show a significant improvement in survival in this elderly cohort, in contrast with their younger counterparts [5]. Only with the introduction of thalidomide, lenalidomide and bortezomib was a significant therapeutic step forward made for elderly myeloma patients.

The regimens

Based on these novel agents, several regimens are considered as standard of care for first-line treatment in elderly MM patients.

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■ Thalidomide based

Six large prospective Phase III trials evaluated the benefit of the addition of thalidomide to the standard MP regimen. Although the design of these studies was different in terms of thalidomide dosing and treatment duration, a meta-analysis of these six trials including 1685 individual patient data, confirmed a significant improvement in anti-myeloma response and PFS by the addition of thalidomide to MP. Most importantly, OS was prolonged by 20% (or 6.6 months) in the melphalan plus prednisone with thalidomide (MPT) arm compared with the more conventional MP approach [6]. Based on these trials, MPT can be considered as a standard for first-line treatment in elderly MM patients. MPT is given orally, which is an advantage especially for elderly and frail patients. However, prolonged use of thalidomide is inevitably associated with peripheral neuropathy (PN) in the majority of patients [7]. Other thalidomide-related side effects, such as constipation, somnolence and tremor, frequently preclude an optimal dosing of this drug in the geriatric population.

■ Bortezomib based

Bortezomib has currently become a backbone for front-line therapy in MM. For elderly patients, strong evidence for clinical benefit has been provided by the so called VISTA study comparing MP with bortezomib plus MP (VMP) [8]. Unprecedented complete responses were observed with the VMP regimen. A recent update after a median follow-up of 5 years, confirmed a significant and durable reduction in death of 31% in the VMP arm compared with MP. This survival benefit was also maintained in several prespecified subgroups such as in patients 75 years or older [9]. However, the standard VMP regimen is intensive in terms of hospital visits and is associated with an important rate of treatment discontinuation, particularly because of PN. In that regard, very elderly or frail patients benefit more from a ‘VMP light’ regimen with once weekly administration of bortezomib, resulting in significantly lower rates of PN, allowing for a higher continuation rate without significant loss of efficacy [10]. The subcutaneous use of bortezomib adds to this benefit by further reducing the neurotoxicity of this drug [11].

■ Lenalidomide based

Lenalidomide plus dexamethasone (Len-dex), one of the most commonly used regimens in relapsed MM, is expected to become another standard of front-line MM treatment in the near future [12,13,101]. Compared with thalidomide, lenalidomide is more potent and associated with less toxicity. The results of prospective Phase III studies in front-line treatment comparing Len-dex with other active regimens are soon to be published. Given the positive results with MPT, an alkylator-based combination of MP with lenalidomide (MPR) was logical for exploration. Although MPR increases the anti-myeloma response rates, excess hematological toxicity precludes its use in very elderly patients [13].

How much is enough?

Doublet, triplet or even quadruplet [14] combinations of anti-myeloma drugs have been evaluated in elderly patients, and a major conclusion from all of these trials is that one treatment size does not fit all patients. Those between 65 and 75 years of age and in good general health are the better candidates for the more intensive combinations like standard VMP or VMP plus thalidomide. However, comorbidities, disability and frailty increase steadily with age, and should be

taken into account in therapeutic decision making [15]. Moreover, very elderly or frail patients are frequently under-represented in clinical trials. A recent retrospective analysis from four large European Phase III studies in elderly MM patients revealed that at the age of 75 years or above, the presence of renal failure at diagnosis, and severe treatment-related complications such as infections, cardiac or gastrointestinal toxicities, significantly increase the risk of death, particularly during the initial treatment months [16]. Therefore, screening for vulnerability and comorbidities at diagnosis will help in treatment optimization by choosing a dose-adjusted, novel-agent-based treatment approach. Possible regimens for this subgroup include for instance VMP once weekly, MPT, or Len–dex with lower drug doses. Trying to avoid serious toxicities is the best guarantee for treatment continuation in the elderly age cohort [17]. This requires frequent follow-up visits with appropriate measures to preserve organ functions and prevent treatment-related toxicities.

To continue or not?

With the availability of potent antimyeloma drugs such as lenalidomide that can be continued for prolonged intervals without cumulative toxicity, the debate about maintenance treatment in first-line MM treatment is still ongoing. For example, after induction with MPR, a landmark analysis showed a 66% reduction in the risk of progression with lenalidomide maintenance [13]. This benefit of maintenance treatment was independent of age. Despite these promising results, no OS benefit could be shown for the study arm with lenalidomide maintenance, most likely because of the availability of novel agent-based rescue therapies at relapse. Similar observations of prolonged PFS without OS benefit were made with bortezomib-based maintenance treatment regimens [18]. In that regard, one should not forget that clinical benefit for a patient is not only expressed by the number of months without disease progression, but also by the interval without treatment- or disease-related symptoms, or without frequent hospital visits. Additionally, one can expect that health authorities and insurance providers will scrutinize these results on

maintenance or continuous treatment, given the extreme high cost of some of the novel agents.

When relapse occurs

Despite the progress achieved with first-line treatment, relapse is the ultimate fate of the majority of MM patients. Depending on the initial response, treatment-free interval, drug-related toxicities and the general condition of the patients, one can choose to retreat with the initial regimen, or to switch drug classes. For instance, a patient initially treated with bortezomib can switch to lenalidomide, and *vice versa* [19]. The odyssey of myeloma drug discovery is still ongoing with newer agents in several phases of clinical development. Second-generation proteasome inhibitors such as carfilzomib and the immunomodulatory drug pomalidomide are already US FDA-approved in the relapsed setting and expected to receive their European license in the near future. Other proteasome inhibitors such as MLN9708 look promising, not at least for their convenience of oral dosing.

In conclusion, there is ample clinical evidence to argue against a fatalistic approach in elderly MM patients. Their current OS ranges between 30 and 56 months and is still improving. A novel agent-based regimen should be the treatment of choice for first-line treatment, whenever these drugs are available. Optimization of myeloma treatment in a geriatric population requires a rational approach based on comorbidities and vulnerability and appropriate antimyeloma drug dosing. Treatment individualization in combination with the right supportive measures to prevent disease- and treatment-related toxicities will maximize a patient's chance for prolonged survival with maintenance of a good quality of life.

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■ Website

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