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Tretatment Approach of Nontransplant Patients with Multiple Myeloma

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ABSTRACT

Multiple myeloma is still an incurable disease with pattern of regression and remission followed by multiple relapses raising from the residual myeloma cells surviving even in the patients who achieve complete clinical response to treatment. In recent years there is a huge improvement in treatment of patients with multiple myeloma. The milestones of these improvement are: autologous transplantation and high-dose melphalan, imunomodulating drugs (thalidomide, lenalidomide), proteosom inhibitors (bortesomib, carfilzomib). The most significant improvement in overall survival has been achieved in the patients younger than 65 years. So, the major challenge for hematologist is to translate this improvement in the elderly patients with multiple myeloma. Today, physicians are able to offer wider variety of treatment options for elderly patients with multiple myeloma. Therapeutic options should be tailored and personalized according to patient's characteristics by balancing efficacy and toxicity of each drug which is especially important for elderly patients. In the mode of sequencing treatment for elderly patients with multiple myeloma, our goal is to achieve and maintain maximal response while limiting treatment -related toxicities as much as possible. Second-generation novel agent, such as carfilzomib, pomalidomide, elotuzumab, bendamustine are currently being evaluated as an option to improve treatment outcome in elderly patients.
Key words: multiple myeloma, treatment, transplant noneligible patients.

Myeloma multiplex is a malignant disorder first recognized in the 19th century and at that time point was described as "mollities ossium" accompanied by the presence of Bence Jones protein in urine. At that time there was no effective treatment and median overall survival was only short: a few months. Over the time, especially over the past decade, many advances in myeloma treatment have been made and improvement of the median overall survival have been achieved. But, myeloma multiplex is still considered incurable disease (1, 2).

Myeloma multiplex is a malignant disorder that arises from the malignant proliferation of plasma cell and is characterized by the presence of at least 10% clonal bone marrow plasma cells and serum and/or urinary monoclonal protein. Myeloma multiplex accounts for 1% of all types of cancers and is the second most common hematologic neoplasm, approximately 13% for all hematologic malignances. Myeloma multiplex is considered as a disease of elderly reflected by the average age at diagnosis 70 years, with 37% of patients younger than 65 years, 26% aged 65 to 74 years, and 37% older than 75years (3, 4, 5).

Patient with myeloma multiplex could be diagnosed as symptomatic or asymptomatic disease. Patients with a symptomatic disease should be treated immediately, and the mainstay of asymptomatic disease is still an observation. Symptomatic disease could be defined with so called CRAB features: C- hypercalcemia (>11.5mg/dl (2.65mmol/l); R-renal failure (serum creatinin >mg/dl; 1.73mmol/l); A-anemia (hemoglobin <10g/dl; 12.5 mmol/l) or 2 g/dl; 1.25mmol/l below the lower limit of normal; and B-bone disease (lytic lesions, severe osteopenia, or pathologic fractures). Patients are stratified into three risk groups according to the International Staging system (ISS). This system defines three risk groups based on serum beta 2 micro globulin and albumin levels at diagnosis. High-risk disease and poor prognosis are defined with the presence of high levels of serum beta2 micro globulin (stage III) (6).

Nowadays, chromosomal abnormalities t(4;14), t(14;16) and t(14;20) chomosome 1 abnormalities and del17 detected by fluorescent in situ hybridization (FISH) are associated with poor prognosis. Hiperdiplpdy, t (11;14), t (6,14), are associated with good prognosis and can be considered "standard risk" (7, 8, 9).

Initial therapy for multiple myeloma depends to a certain extent on patients characteristics such as: eligibility for autologous stem cell transplantation per se; age and co-morbidities. The role of induction therapy is to induce remission, but patient's characteristics have a significant role in the initial treatment approach. Goals of treatment are: to eradicate the tumor clone, including cancer stem cell, to search for an appropriate balance between efficacy and toxicity with three different but complementary aims: quality of life, survival prolongation and eventually the dream of cure. This can be achieved if we use appropriate tools to evaluate treatment efficacy. Achieving the lowest level of

minimal residual disease can be an important goal of therapy, a step in the path to cure (9, 10).

Today, treatment goals in myeloma patients are shifting and the goal of therapy in elderly patients is to achieve and maintain maximal response. Many believe that multiple myeloma can be converted into a chronic disease and that a functional cure maybe a realistic goal. Attainment of complete remission at any time point during treatment is associated with improvement outcome; so it is likely to be established as a goal of therapy (11, 12, 13, 14). The increasing number of treatment possibilities as an optimal therapeutic strategy improve patient outcome. Physicians have the opportunity to choose the best treatment regimen according to patient characteristics, while limiting treatment – related toxicities as much as possible. In elderly patients optimal treatment should be always balance efficacy and toxicity (2, 15, 16).

Initial therapy for multiple myeloma depends on eligibility for high-dose therapy and autologous stem cell transplant (HDT-ASCT). (11,17) In many European countries, elderly patients (older than 65) are generally considered ineligible for autologous stem cell transplantation (ASCT) (18). In past times in practice, patients were stratified to those who are transplant eligible and consolidated with high-dose melphalan/SCT and those who were transplant ineligible and received oral melphalan with prednisolone (MP). This stratification has been made in the era of conventional therapy where response rates to the induction therapy were poor and the goal was achievement of partial response and prevention of organ damage. So, in contrast, today we considered that biological age and chronological age do not always correspond, and a greater emphasis should be placed on the former rather than the latter (19). CR is a good surrogate end point for survival in transplant-ineligible patients and novel drugs have been incorporated into the treatment of non-transplant candidates (20). Patients are generally considered eligible for ASCT if they have good performance status, no-comorbidities, and normal cardiac, pulmonary, liver and renal function. Patients older than 75 years or vulnerable ones are more susceptible to adverse events and in this setting we are looking for less toxic regimens and appropriate dose reductions should be adopted (9, 10, 21). Even, ASCT with a reduced melpahlan conditioning dose is well tolerated by the selected population of patients up to the age of 75 in good clinical conditions. Until novel agents were introduced, for more than 40 years the combination of melpahalan and prednisone (MP) was considered the standard approach for transplant –ineligible patients, with PFS of approximately 18 months and 2-3 years (at best) overall survival in the population treated with MP. A meta-analysis including 27 randomized studies compared MP with other chemotherapy-containing regimens (22). The introduction of novel agents has challenged this combination and new and more effective combination is available.

Six randomized phase III studies have shown that the combination melphalan-prednisone-thalidomide (MPT) is superior to MP in terms of response and progression-free survival, but it was translated into improved survival in the 2 IFM studies (23-28). An efficacy meta-analysis of the six MPT trials including 1685 patients was conducted and has showed that the addition of thalidomide to MP significantly prolonged both PFS and extended OS by 20%–39 months compared to MP- 33 months (29). The meta–analysis further confirmed the progression-free survival advantage achieved with MPT. So, MPT is therefore regarded as a new standard of care in transplant ineligible patients.

For selected elderly patients, particularly for standard risk patients with favorable FISH, CTD is a feasible approach. A phase III assessed the role of thalidomide in combination with different alkylating agent and steroid than those commonly used, respectively cyclophosphamide and dexamethasone with an attenuated schedule (CTDa). Despite a deeper response, no differences were noted in median PFS and OS between patients treated with CTDa and MP (30).

Lenalidomide is an immunomodulatory drug with higher potency than its analogue thalidomide and without sedative or neurotoxic adverse effects. Lenalidomide showed to be safe and effective in relapsed/refractory multiple myeloma patients, as well as in newly diagnosed multiple myeloma patients.

The phase III trial RD (lenalidomide plus high-dose dexamethason) versus Rd (lenalidomide plus low-dose dexamethason) included newly diagnosed multiple myeloma patients both eligible and ineligible for autologus stem cell transplantation. Rd seems preferable for elderly patients because has significantly longer 1-year overall survival, particularly evident in patients older than 65 years of age and can be considered a valid therapeutic option for elderly newly diagnosed myeloma patients. RD remains a good option for patients with renal failure, hypercalcemia, pain or spinal cord compression because more adverse events occurred when RD was given compared with Rd (31).

The role of lenalidomide was assessed in a recent phase III study that compared melphalan-prednisone-lenalidomide followed by lenalidomide maintenance (MPR-R), with MPR and MP. MPR-R significantly improved median progression-free survival compared with MPR and MP (31 months versus 14 months vs. 13 months; $p<0.001$), which means that MPR-R reduced the risk of progression by 51% and 60% compared with MPR and MP. Lenalidomide maintenance was well tolerated with few reported incidence of grade ¾ adverse events and second cancer. However the benefit associated with MPR-R outweigh the increased risk of second primary malignancies (32, 33).

VISTA study compared MP versus VMP and proved that addition of bortezomib to MP is rational, because responses, time to progression and survival were significantly higher with VMP (34, 35).

In the Spanish PETHEMA trial a cohort of 260 patients older than 65, transplant ineligible, were randomized to receive induction treatment with 6 cycles of bortezomib-thalidomeide-prednisone VTP, or VMP considered as more gentle approach where melphalan is used instead of thalidomide(36). Both regimens led to high ORR rate (81%and 80%), but there were more adverse events among patients with VDT. VMP with once-weekly schedule of botezomib should be preferred to VTP as induction for elderly multiple myeloma patients. One-weekly bortezomib was scheduled instead of standard twice-weekly administration to reduce adverse events, especially neuropathy associated with bortezomib administration.

The combination of bortezomib-lenalidomide-dexamethasone (VRD) was evaluated in both young and elderly patients with multiple myeloma.

The addition of thalidomide to the new treatment standard with VMP followed by bortezomib-thalidomide maintenance is valid alternative with 3-years overall survival 565 with VMP-

VT compared with 41% with VMP. VMP-VT with once weekly bortezomib seems to be a valid alternative for elderly patients particularly those younger than 75 years, where there is the same efficacy, but without additional toxicity, particular peripheral neuropathy (37).

A sequential approach consisting of an induction regimen associated with a high rate of complete response, followed by consolidation, maintenance therapy, induce a profound cytoreduction and delays relapse, thus improving survival as a therapy approach that minimized toxicity maximized quality of life and emphasized patient's preference. This choice of treatment strategy improve outcome and prevent the occurrence of relapse with a continuous treatment keeping residual disease under control. The international MM015 phase III study assessed the role of lenalidomide given in maintenance. Having this in mind MPR followed by lenalidomide maintenance emerges as a new standard treatment option for elderly multiple myeloma patients. Another treatment option for elderly patients with impressive result is more intensive regimen VMPT followed by VT maintenance. Bortezomib showed same efficacy with decreased toxicity administrated in a new schedule from twice to once weekly (38).

As we already emphasized, the choice among these regimens should be based on the patient's characteristics. For elderly patients with renal impairment bortezomib or thalidomide containing regiment is considered the best treatment option, because lenalidomide is excreted by the kidneys. In such a case dose of lenalidomide should be reduced according to creatinin clearance. Despite that, for patients with peripheral neuropathy lenalidomide is considered as the best treatment option because of the reduced neurological toxicity. In elderly patients there is an increased risk of treatment-related adverse events in response to novel agent-containing regimens. Clinicians should be aware and proposed guidelines for dose reduction of novel agents and protocol modification in elderly should be followed in clinical practice for elderly patients with multiple myeloma to optimize outcome. So, there is an attempt to personalize the therapy in multiple myeloma according to patient age and vulnerability proposed by European Myeloma Network (EMN) (16, 17, 39).

Multiple myeloma is still an incurable disease with pattern of regression and remission followed by multiple relapses raising from the residual myeloma cells surviving even in the patients who achieve complete clinical response to treatment. New anti-myeloma drugs change treatment paradigm providing both tumor reduction and tumor suppression. There is so much progress, but still many unsolved questions. Today, physicians are able to offer wider variety of treatment options for both young and elderly patients with multiple myeloma. Therapeutic options should be tailored and personalized according to patient's characteristics by balancing efficacy and toxicity of each drug which is especially important for elderly patients. In the mode of sequencing treatment for elderly patients with multiple myeloma, our goal is to achieve and maintain maximal response while limiting treatment -related toxicities as much as possible. Second-generation novel agent, such as carfilzomib, pomalidomide, elotuzumab, bendamustine are currently being evaluated as an option to improve treatment outcome in elderly pateints (2).

CONFLICT OF INTEREST: NONE DECLARED.

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