MPe
Myeloma
Patients
Europe

Conference Report

European Haematology Association Annual Meeting (EHA) 2016

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Introduction

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The most important scientific meeting about haematological diseases in Europe is the annual meeting of the European Haematology Association (EHA) that took place in Vienna in June 2016. This supplement presents the highlights relating to key developments in myeloma during this conference.

Diagnosis criteria update for multiple myeloma

The diagnostic criteria for myeloma have recently been updated to include some myeloma patients not showing any of the C.R.A.B. criteria symptoms (C for hypercalcaemia, R for renal impairment, A for anaemia, and B for bone injuries) or other symptoms of multiple myeloma. Thanks to the new guidelines, physicians can diagnose this disease taking into account the following biomarkers of malignancy:

- Clonal bone marrow plasma cell percentage ≥60%
- Involved/uninvolved serum free light chain ratios ≥100
- >1 focal lesions on magnetic resonance imaging (MRI) studies

Asymptomatic or smoldering myeloma patients are a very heterogenous group. Within this group of patients, haematologists can identify patients with low, intermediate, high and ultra-high risk of progression and determine if they need any treatment.

So far, the standard management for smoldering myeloma patients was just following them up on a regular basis in order to determine when the disease begins to progress. According to these new guidelines, follow-up is recommended for patients with a low and intermediate risk of progression while patients with ultra-high risk of progression should be considered as symptomatic myeloma patients and start being treated immediately.

If the patient has a high risk of progression to myeloma, the standard of care is a close follow-up, but they are also suitable candidates for clinical trials and sometimes candidates for early treatment as well. Currently, there is some ongoing research, such as the "QuiRedex" clinical trial, which evaluates the early treatment of this group of patients. The QuiRedex results show that the probability of progression to myeloma can be significantly reduced. Thus, the early treatment for high-risk smouldering myeloma can be an optimal therapy approach.

The multicentre, open-label, randomised phase III clinical trial, QuiRedex, has evaluated the efficacy of treatment with lenalidomide and dexamethasone in patients with high risk of progression to myeloma. This research compares this combination with the current standard of care, that is, active surveillance. The trial was completed and recently updated with a median follow-up of 72 months. The results showed that patients who received the combination of lenalidomide and dexamethasone were able to significantly reduce the probability of progression to symptomatic myeloma (the median follow-up is 75 months to progression).

The diagnostic criteria for myeloma have been recently updated to include some myeloma patients not showing any of the C.R.A.B. criteria symptoms (hypercalcemia, renal impairment, anaemia or bone injuries).

Complete response and minimal residual disease

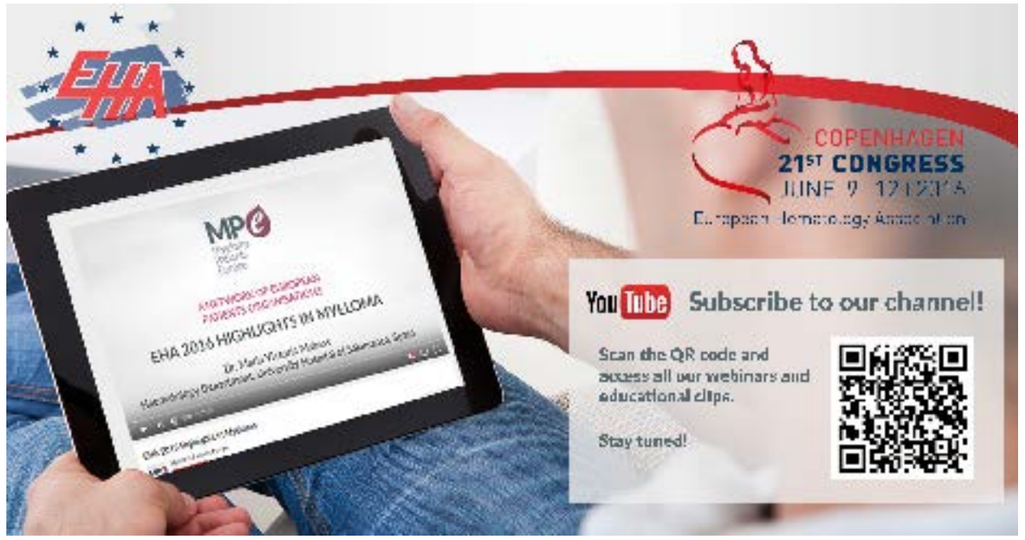
"Patients who achieve a complete response have a significantly longer time to progression and longer progression-free survival".

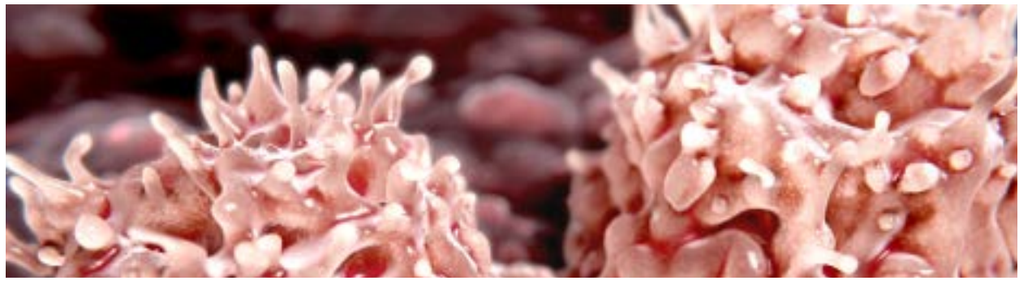
Dr. María Victoria Mateos, University Hospital of Salamanca, Spain

During the EHA Annual Meeting, markers of prognosis such as complete response and minimal residual disease were discussed.

According to Dr María Victoria Mateos, Department of Haematology of the University Hospital of Salamanca (Spain), complete response is one of the most important goals doctors have to achieve in multiple myeloma treatment. *"The depth of response is related to the time to progression and also to overall survival. Patients who achieve a complete response have a significantly longer time to progression and longer progression-free survival. That is the reason why this marker is important for us, but we always have to balance it with an optimal quality of life".*

In addition, although the evaluation of minimal residual disease into the bone marrow is an important goal, it is critically relevant to evaluate it also outside of the bone marrow. To evaluate this parameter, imaging assessments are being used more and more frequently. *"We have to evaluate minimal residual disease also out of the bone marrow and this is the reason why now more imaging assessments are being done in myeloma patients. If PET-CT is negative after transplant, the outcome is much better because minimal residual disease evaluation is a relevant prognostic factor in the management of newly diagnosed multiple myeloma (NDMM)".*





Transplant candidate patient

Whenever possible, autologous stem cell transplantation (ASCT) is currently the standard of care in myeloma for eligible patients – patients without severe comorbidities and under 65 years of age. The complete treatment includes four different parts: induction, transplant, consolidation and maintenance therapy. Although induction with vincristine-doxorubicin-dexamethasone (VAD) – "A" in VAD stands for Adriamycine, which is the commercial name of doxorubicin – used to be the standard of care, new agents have been incorporated to the treatment to provide a significant overall response rate but also an important higher complete response rate. According to Dr Mateos, "*nowadays, thalidomide is the most used immunomodulatory drug for induction, but in the near future lenalidomide in combination with bortezomib and dexamethasone will be the standard of care in this stage of the treatment. With this induction regime, approximately 30% of the patients could achieve a complete response*".

However, the role of lenalidomide is not just relevant as an induction therapy, but also as a maintenance therapy, where it seems to be crucial according to the results of a meta-analysis presented at the EHA meeting. So far, the maintenance therapy, which should be administered for a prolonged period, is based on thalidomide. One of the main side effects of this drug when used as a maintenance therapy is peripheral neuropathy. Lenalidomide is a second generation immunomodulatory drug that has been evaluated in three different large phase III, randomised trials compared with placebo after ASCT as a maintenance therapy. Lenalidomide shows in this meta-analysis a 26% reduction in the risk of death representing an estimated 2.5-years increase in median survival. "*This results are important for European patients because probably, thanks to this meta-analysis, authorities will consider the approval of lenalidomide as maintenance therapy after autologous stem cell transplantation*", explained Dr Mateos.

The role of maintenance therapy after ASCT is still being discussed. There are many questions to answer such as how long patients should receive maintenance therapy, who should receive this kind of treatment and how to monitor the efficacy of the therapy. "*There is definitively a role for maintenance therapy but nowadays some caveats remains uncertain,*" said Dr Mateos.

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Treatment of non-transplant candidate myeloma patients

As mentioned above, autologous stem cell transplantation is currently the standard of care in myeloma for eligible patients. Patients are generally considered eligible for this procedure if they have good performance status, no comorbidities, and normal cardiac, pulmonary, liver and renal function. Elderly patients or vulnerable ones are more susceptible to adverse events and they usually receive less toxic regimens and appropriate dose reductions should be adopted.

Most non-transplant candidate patients are over 65 years old. Overall survival in this group of patients has been doubled due to the introduction of novel agents based on several drug combinations. However, this group of elderly patients is quite heterogenous, and doctors can differentiate between those who have good general health (no comorbidities, generally fit) and those who haven't. For that reason, incorporating geriatric assessments into routine practice is increasingly necessary to classify this group of patients as fit, unfit or frail, regardless of their age.

The goal in the treatment of non-transplant candidate myeloma patients is to achieve a high-quality, sustained and complete response with an acceptable toxicity as well as a good quality of life. For that reason, tolerability in elderly patients was another topic discussed at EHA 2016.
Melphalan plus prednisone (MP) and bortezomib combination is one of the most frequent standard of care used upfront for newly diagnosed elderly multiple myeloma (eNDMM) patients. Significant improvements, such as a weekly schedule or sub-cutaneous administration, have been done in order to increase the tolerability of this combination. Lenalidomide plus dexamethasone is another standard of care for this group of patients given as continuous therapy until disease progression or unacceptable toxicity. The use of new combinations such as carfilzomib with melphalan and prednisone could improve tolerability in elderly patients. According to the data presented during the EHA meeting, carfilzomib, a novel generation proteasome inhibitor, used on a weekly schedule, allows the dose to be increased, given its positive safety profile.

The clinical trial Carmysap , a phase I/II multicentre open-label single-arm study, has the objective to determine the maximum tolerated dose (MTD) of carfilzomib administered once weekly in combination with melphalan and prednisone (KMP) – K in KMP stands for Kyprolis, the commercial name of carfilzomib – followed by weekly carfilzomib maintenance in elderly patients with newly-diagnosed MM. A total of 30 patients were treated with doses of 36, 45, 56, and 70mg/m². The research concludes that the maximum tolerated dose (MTD) of carfilzomib has not been reached and 70mg/m² should be the recommended phase 2 dose.

New combinations in relapsed or refractory multiple myeloma (RRMM)

The most important advances presented at the EHA meeting were focused on relapsed or refractory myeloma treatment (RRMM). New drug combinations are being added to the haematologists' therapeutic armoury to get better results with lower toxicity rates.

"During the last year many different new combinations have been approved by the Food and Drug Administration (FDA) in the United States and also in Europe. The European Medicines Agency (EMA) has approved pomalidomide, panobinostat, carfilzomib, elotuzumab and, more recently, daratumumab, the first monoclonal antibody effective as a simple agent for the treatment of multiple myeloma," said Dr Mateos.

In order to choose the best possible treatment, it is important to evaluate the specific situation of every individual patient (type of relapse, efficacy of previous treatments, toxicity of previous treatments and further options). *"We have to consider that most of the patients are receiving bortezomib-based regimes as the first line of treatment. This is probably the most common induction regimen used in Europe. So when our patients relapse, lenalidomide and dexamethasone are the standard of care to be used at first as a rescue setting."*

Although haematologists still consider lenalidomide and dexamethasone as one of the standards of care in this stage of the disease, thanks to the new combinations physicians are considering four other new combinations based in lenalidomidee and dexamethasone plus other drug. These four combinations could replace lenalidomide and dexamethasone alone as a standard of care.

Carfilzomib plus lenalidomide and dexamethasone

The addition of carfilzomib resulted in significant benefits in terms of progression-free survival but also in terms of complete response. According to the ASPIRE study data, 32% of the patients achieved a complete response with this rescue therapy. This is the reason why this combination is now one of the new standards of care at the moment of relapse.

Elotuzumab plus lenalidomide and dexamethasone

Elotuzumab is a monoclonal antibody. The benefits of adding this drug to lenalidomide and dexamethasone was evident in terms of progression-free survival observed even after three years of follow-up. In addition, this combination showed a benefit in terms of time to next therapy – almost three years – which is especially relevant for this group of patients.

Ixazomib plus lenalidomide and dexamethasone

In addition to its efficacy, the great advantage of ixazomib is its route of administration along with its safety profile. Ixazomib and also lenalidomide and dexamethasone are oral agents, therefore an important option for patients who are unable to go to the hospital regularly. Dr Mateos said: *"The combination of these three drugs was superior in terms of progression-free survival compared with placebo plus lenalidomide and dexamethasone. The complete response rate was also double than the control arm. This treatment represents a full oral combination effective in the management of patients at the moment of progression or relapse"*. For all these reasons, Dr Mateos said that this triple oral drug combination has the potential to become a standard of care for this particular group of patients.

Daratumumab plus lenalidomide and dexamethasone

Daratumumab is a monoclonal antibody approved as a single agent for the treatment of myeloma at the moment of relapse. "*A benefit in terms of progression-free survival was evident with this drug, but when daratumumab is added to lenalidomide the reduction in the risk of disease progression or death is 63%. I would say that this is the best progression-free survival so far reported for relapsed and refractory myeloma patients*", said Dr. Mateos.

This remarkable benefit was shown in the POLLUX study , an open-label, randomised phase III study conducted in 18 countries. This research evaluated the combination of daratumumab plus lenalidomide and dexamethasone (daratumumab group) compared with lenalidomide and dexamethasone (control group) in 569 patients with RRMM who received at least one prior line of therapy. At the preplanned interim analysis, an unprecedented 63% reduction in the risk of progression or death was shown in the daratumumab group compared with the control group, leading to early unblinding of the study. More patients achieved an overall response in the daratumumab group compared with the control group (93% vs 76%, P <0.0001). Deep and durable responses were significantly more frequent in the daratumumab group, with higher rates of very good partial response or better (76% vs 44%, P <0.0001) and a more than doubling of complete response or better (43% vs 19%, P <0.0001).

"*In my opinion, the current situation is optimal for physicians and also for patients because we are going to be able to individualise the treatment much more at the moment of relapse using one or another combination according to the type of relapse, biochemical, disease aggressiveness, age, number of prior lines of therapy...*", said Dr Mateos.

Highlights

- The diagnostic criteria for myeloma have been recently updated to include some myeloma patients not showing any of the C.R.A.B. criteria symptoms (hypercalcemia, renal impairment, anaemia or bone injuries). According to these new guidelines, asymptomatic patients with ultra-high risk of progression should be considered as symptomatic myeloma patients and start being treated immediately.

- Achieving minimal residual disease (MRD) negative status is even more relevant than complete response for the prognosis of myeloma. It is a relevant prognostic factor in the management of newly diagnosed multiple myeloma (NDMM) and also probably at early relapses.

- According to the data presented in EHA, new drug combinations are being added to the haematologists' therapeutic armoury to get better results with lower toxicity rates. Carfilzomib, daratumumab, elotuzumab and ixazomib, all of them plus lenalidomide and dexamethasone are the new combinations that could replace lenalidomide and dexamethasone alone as a standard of care.

- The POLLUX study showed that when daratumumab is added to lenalidomide the reduction in the risk of disease progression or death is 63%, the best progression-free survival so far reported for relapsed and refractory myeloma patients.

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