

53rd ASH meeting (2011) in San Diego: Multiple Myeloma (MM) update

This year, the 2011 ASH meeting gathered the MM specialists in the city of San Diego, Southern California. It was more than worth to undertake the long trip to get there and learn about the continuous progress made in the knowledge and treatment of our disease.

A personalized treatment approach for MM patients is definitely the way forward for the future.

The sessions at the meeting not only presented data on new therapies (information that the reader will find in this report), they also included discussions on prognostic factors that possibly predict the outcome of myeloma treatment in the different subgroups of patients. The international Staging System (ISS), the presence of chromosomal abnormalities (measured by FISH technique) and the achievement of a complete remission (CR) once treatment has been started are traditionally used to predict the outcome of the therapy. Newer prognostic tools have been explored and further discussed at the conference such as gene-expression profiling and proliferative indices. Also, the presence of CR may not be sufficient to predict long-term outcome. Indeed, new sensitive techniques can detect minimal residual disease (MRD)¹. The absence of MRD seems an important factor in predicting long-term treatment results. In this context of personalized treatment, it was stressed that specific strategies should be developed for the different subgroups of MM patients, particularly for high-risk patients (with a special emphasis on patients with del17p). As a patient, I cannot say that the overview and choice of treatment options is becoming easier to understand but I am convinced that treatment possibilities are getting better! Ready to learn more about it?

1. Treatment of patients, eligible for transplantation

Even in the era of novel agents, high dose therapy with autologous stem cell transplantation (ASCT) remains the first-line treatment of choice for the younger and/or fitter myeloma patient confirmed Prof. Palumbo. But the integration of the novel agents in the different sequences of transplantation improves remarkably the results of high dose therapy and ASCT:

- during the induction therapy before high dose therapy and transplantation
- after the transplantation as consolidation and/or maintenance therapy

1.1 Induction treatment:

Response obtained by induction therapy before high dose therapy and ASCT has shown to improve the long-term outcome after the transplantation. Many studies, looking for the optimal induction regimen were presented but it must be said that it is not easy to interpret the impact of novel induction regimens alone on the post transplantation outcome because many patients in trials are now also treated with consolidation and/or maintenance therapy which further improves transplantation results (see 1.2). Although more research is necessary to define the optimal induction therapy and the duration of it, it is undeniable that the novel agents - thalidomide, lenalidomide (Revlimid®) and bortezomib (Velcade®) - are the major actors in the induction treatment.

¹ MRD is the name given to a small number of myeloma cells that remain detectable in the patient by using special techniques (one example is flow cytometry), even when traditional tests indicate a complete response to treatment.

Dr. Reece gave some examples of important studies², which demonstrate the efficacy of induction therapy including a novel agent. Next, she showed with subsequent studies³ that adding a second novel agent to the induction regimens further improves their efficacy. An interesting induction regimen where two novel agents are combined is RVD (Revlimid®, Velcade®, dexamethasone). This induction combination leads to high response rates: an overall response rate of 100% with a very good partial response (VGPR) rate of 76% and complete response/near complete response (CR/nCR) rate of 40% (Richardson et al).

In Europe, the bortezomib-based induction regimen is getting into the standard of care and is especially appropriate in patients with cytogenetic abnormalities such as t(4;14). Lenalidomide-based induction (which has the advantage of being administered orally) is more used in the United States as an effective induction regimen, but results of ongoing studies are awaited in Europe. Up to now, bortezomib based induction therapies have not yet been compared with those based on lenalidomide in randomized trials but both proved to be valuable induction regimens before high dose therapy and ASCT. For patients with high-risk disease, induction therapy including bortezomib, eventually supplemented by an IMiD (thalidomide or lenalidomide) is probably the treatment of choice.

1.2 Consolidation/Maintenance therapy:

The difference between consolidation and maintenance therapy is not always clear but consolidation therapy is given after the high dose therapy and ASCT to consolidate the results and improve the depth of the response. Maintenance therapy is given to prevent relapse of the myeloma. At the congress, a lot of data was presented on maintenance therapy.

1.2.1 Maintenance with thalidomide in patients, eligible for transplantation

Maintenance treatment with thalidomide after ASCT has been studied extensively in several trials (examples: see report ASH 2010) and is associated with longer progression free survival (PFS). However, over extended periods of time, patients may suffer from debilitating side effects (such as neuropathy), which can lead to discontinuation of the treatment.

This is the reason why researchers started to explore the use of the newer immunomodulatory drug lenalidomide (Revlimid®) and the proteasome inhibitor bortezomib (Velcade®) as possible maintenance therapies.

1.2.2 Maintenance with lenalidomide (Revlimid®) in patients, eligible for transplantation

In my report of the ASH meeting of last year, 2 important studies with lenalidomide maintenance (versus placebo) were presented:

² Examples of studies with induction therapy that includes a novel agent:

- HOVON 50 study: TAD (thalidomide, Adriamycin®, dexamethasone) versus VAD (vincristine, Adriamycin®, dexamethasone)
- IFM 2005-02 study: BD (bortezomib, dexamethasone) versus VAD (vincristine, Adriamycin®, dexamethasone)
- HOVON-65/GMMG-HD4: VAD (vincristine, Adriamycin®, dexamethasone) versus PAD (proteasome inhibitor of Velcade®, Adriamycin®, dexamethasone)
- PETHEMA/GEM05M: VBMCP/VBAD/B (a multistep combination therapy: vincristine, carmustine or BCNU, cyclophosphamide, melphalan, prednisone, dexamethasone, and bortezomib) versus thalidomide+dexamethasone
- Lenalidomide with dexamethasone (low and high dose)

³ Examples of studies with induction therapy that includes two novel agents:

- GIMEMA MMY-3006: VTD (Velcade®, thalidomide, dexamethasone) versus thalidomide + dexamethasone
- IFM 2007-02: BD (bortezomib, dexamethasone) versus VTD (bortezomib or Velcade®, thalidomide, dexamethasone)

- the IFM 2005-02 trial (a French study)
- the CALGB 100104 trial (a US study)

Although these trials did not have the same design⁴, both studies consistently show superior PFS rates in the lenalidomide maintenance arm compared to the patients who received a placebo.

Moreover, recent data from the CALGB trial teach us that patients who were treated with lenalidomide maintenance have a survival benefit.

Those who read last year's report might recall that a possible signal of occurrence of Second Primary Malignancies (SPMs)⁵ was observed in patients who were on lenalidomide maintenance.

The medical community has taken this signal seriously and a lot of research has been done in the year 2011. At the same time, the EMA (European Medicines Agency) reviewed all the existing data on the use of lenalidomide and the occurrence of SPMs. Scientists agree that the risk of a SPM remains small and data suggest that one of the possible risk factors might be the use of particular types of chemotherapy in combination with an IMiD.

It was concluded that the benefits of treatment with lenalidomide outweigh the risk of SPMs. In other words, the risk of disease progression (in the absence of lenalidomide treatment) is much more significant than the risk of SPMs. But, the medical community recognizes that further observation and follow-up of the situation is necessary.

1.2.3 Maintenance with bortezomib (Velcade®) in patients, eligible for transplantation

The HOVON 65/GMMG-HD4-trial is the only phase 3 trial in this setting (see also ASH 2010 report).

In this study, patients had different induction regimens: either VAD (vincristine, Adriamycin® and dexamethasone) or PAD (the proteasome inhibitor bortezomib, Adriamycin® and dexamethasone). After ASCT, the VAD group received low-dose thalidomide for 2 years and the PAD group received bortezomib every 2 weeks for 2 years. It is difficult to commend only on the maintenance therapy in this study as the results are to be interpreted in the context of the entire treatment approach but progression free survival (PFS) and overall survival (OS) were clearly superior in the patients, treated with bortezomib (induction and maintenance) and this advantage was even more pronounced in patients with renal problems or with high-risk MM due to unfavorable cytogenetics (such as t(4;14)).

Conclusion:

Currently, the superiority of any particular maintenance therapy needs to be further evaluated but results of large phase 3 trials with lenalidomide maintenance have demonstrated the longest PFS after ASCT to date.

Further research will learn us in the years to come the most appropriate treatments in the different subgroups of MM patients and additional information about long-term outcomes will likely influence post-ASCT treatment.

2. Treatment of patients, non eligible for transplantation

At the congress, a lot of data was presented on research with novel agents in patients who are not eligible for transplantation. Often, these were further updates of big trials we

⁴ The studies had different induction treatments, some patients in the IFM trial had a double transplantation, the patients in the IFM study received first 2 consolidation cycles with lenalidomide at full therapeutic dose (25mg/daily) and then continued with a low dose maintenance therapy with the same drug, whereas the CALGB study started immediately with lenalidomide maintenance after ASCT

⁵ SPM: a new (other) primary cancer developing in a person with a history of cancer

mentioned already in past reports. Some of these trials had an extra focus on maintenance therapy.

- Update VISTA trial: comparing VMP versus MP (San Miguel et al)

This international, multicenter Phase 3 trial got a lot of attention at the 49th ASH congress (see my report of ASH 2008). The initial results of the VISTA trial demonstrated the clear superiority of VMP (Velcade®-melphalan-prednisone) compared to MP (melphalan-prednisone) in terms of response rates, PFS and OS.

Prof. San Miguel now closes the information on this trial and confirms that after 5 years of follow-up, VMP demonstrates a persistent, significant OS benefit compared to MP (a median of 13.3 months increase) in non-transplant patients with previously untreated multiple myeloma. These results are observed in different pre-defined subgroups of patients, including those older than 75 years, patients with advanced stage MM and persons with poor renal function. However, no significant difference was seen in patients with unfavorable cytogenetics.

The follow-up results also focused on a possible occurrence of SPMs. Patients now live much longer and the hypothesis was that we possibly do not know all the long-term consequences of the novel agents. The good news is that the incidence of SPMs in this study is very low, the same in both arms and similar to the occurrence in the general population.

As a consequence, we can say that VMP is a very appropriate treatment for the elderly patient, which clearly prolongs survival with no increased risk of SPMs.

- UPFRONT trial: comparing VD versus VTD versus VMP (Niesvizky et al)

Dr. Niesvizky presented the final results of the community-based UPFRONT study, which compares three different Velcade® regimens for patients with newly diagnosed myeloma who are no transplant candidates: VD (Velcade®-dexamethasone), VTD (Velcade®-thalidomide-dexamethasone) and VMP (Velcade®-melphalan-prednisone). The population studied in this trial had relatively high co-morbidities (other co-existing diseases or conditions).

Dr. Niesvizky concluded that patients who received the double-agent therapy (VD) had similar long-term outcomes compared to the patients who followed a triple therapy (VTD or VMP). Moreover, patients who followed a 3-drug combination treatment needed more dose reductions in order to manage side effects and had a greater tendency to discontinue treatment than the patients who were on VD.

These data suggest that more intensive triplet therapy with VTD or VMP offers little advantage over the twin combination VD in the elderly patients.

The study also highlighted that Velcade® was active in all patient subgroups but results and side effect profile were better in certain patient groups (patients < 75 years, patients with no comorbidities). Although these results show that Velcade® can overcome multiple risk factors, they also highlight once again the ongoing need for improved treatment options for elderly patients and more specifically for subgroups of frailer patients and those with comorbidities.

- Update MM-015 study: comparing MP versus MPR versus MPR-R (Palumbo et al)

In my report of ASH 2010, this trial with a focus on lenalidomide maintenance therapy, was highlighted. Prof. Palumbo now updates the audience with the final results.

The trial compared three treatment options. One group of patients was treated with MP (melphalan and prednisone) and the two other patient groups with MPR (melphalan, prednisone and Revlimid®). Of these last patients, half was subsequently given maintenance therapy with Revlimid® (MPR-R), the other half with placebo. The MP-treated patients received also maintenance therapy with a placebo.

The final results now confirm that Revlimid® maintenance significantly extends progression free survival (median PFS was 31 months in the MPR-R group, 14 months in the MPR group and 13 months for the MP patients).

At last years ASH, the first signal of SPMs showed up in this trial in a very small group of patients, treated with lenalidomide (Revlimid®) maintenance.

In the past months, a lot of attention has been given to this observation (see also 1.2.2).

Prof. Palumbo explained that indeed, there is a slightly higher incidence of SPMs (although the absolute numbers are very small) in the lenalidomide treated patients but that this risk is far outweighed by the benefits of treatment with this medicine. However, further vigilance is warranted concluded the Italian MM specialist.

- GEM2005MAS65: Study comparing VMP versus VTP plus maintenance VT or VP (Mateos et al)

In 2010, the results of the first stage of this study were published in the Lancet Oncology, a leading medical journal. In this first stage, patients received induction therapy based on a weekly dose of bortezomib (Velcade®) in combination with prednisone plus either melphalan (VMP) or thalidomide (VTP) during 6 cycles. VMP and VTP as induction regimens yielded similar overall responses rate (80% and 81%, respectively). After this induction treatment, the second part of the trial randomly assigned patients to maintenance therapy with bortezomib plus prednisone (VP) or bortezomib plus thalidomide (VT).

In San Diego, Dr. Mateos announced the results of this second stage of the study comparing both maintenance regimens, given for up to three years after the induction therapy.

Maintenance therapy increased remarkably the response rates (from 24% after induction therapy to 42% after maintenance therapy).

Although no significant differences between VP and VT were observed, there was a slight trend to better PFS for patients in the VT arm. Patients treated with VT had a bit more side effects than patients in the VP arm, but these were manageable.

Based on these results, Dr. Mateos concluded that a bortezomib based induction scheme, followed by bortezomib maintenance therapy is an attractive treatment scheme for the elderly patient. She also suggested that using the newer IMiD lenalidomide (Revlimid®) instead of thalidomide could reduce side effects and potentially improve the efficacy.

3. Treatment of patients who relapse

I was quite impressed about the dynamic research activity in this setting. A dizzying variety of new agents come close at high speed!

Let's start with the next generation of proteasome inhibitors, medicines belonging to the same class as Velcade®:

- Carfilzomib

The efficacy of carfilzomib, observed in clinical trials, was already described in last year's ASH report. Interesting is that the drug has fewer side effects than Velcade®, more particularly the lower rates of peripheral neuropathy.

At this ASH, further data from three phase 2 studies were presented to the audience. In these trials, carfilzomib was looked at as a single agent or in combination with Revlimid®/dexamethasone or thalidomide/dexamethasone. The combination with lenalidomide was particularly interesting because of the high and rapid response rates, especially in patients with high-risk cytogenetics. Carfilzomib is coming close to joining the available and approved treatment arsenal for MM as the approval process of the drug at the FDA (Food and Drug Administration) is ongoing and an additional current trial (FOCUS trial) will soon give more evidence for the European marketing authorization of the drug by EMA (European Medicines Agency).

- Marizomib

Another new proteasome inhibitor marizomib was introduced by Dr. Richardson who presented combined early data from US and Australian Phase 1 studies in heavily pre-treated patients. One fifth of these patients responded to the treatment. Dr. Richardson suggested that further research should be done with this new agent, alone or in combinations with dexamethasone or Revlimid®.

- A new kid in the family: MLN9708!

Unlike bortezomib, carfilzomib and marizomib which are all given by infusion or injection, this new proteasome inhibitor can be administered orally in capsule form. Many MM patients will appreciate this new way of administration!

Initial results from three early-phase trials are promising.

In two of these early studies (which have as main goal to determine the maximum tolerated dose and the safety of the drug), MLN9708 was studied as a single agent treatment in patients with relapsed and refractory (treatment resistant) patients.

Both studies showed response rates of 13 and 11% respectively and an acceptable toxicity profile. The third early study combined MLN9708 with Revlimid® and dexamethasone and showed that this was a synergistic combination. All patients (100%) in this small trial group had at least a partial response to the treatment, including a very good partial response (VGPR) in 33% and complete response (CR) in 27%. Additionally, the response to treatment was very rapid: after one treatment cycle 93% of the patients reduced their M-protein by 50%.

- Pomalidomide

We familiarized already with this new and promising IMiD at last year's ASH. Further solid evidence from 2 studies (a US and a French one) about the efficacy of this medicine, alone or in combination with dexamethasone was given in San Diego. Long term responses confirmed the high activity of pomalidomide in relapsed/refractory patients. Additional good news is that these responses were also seen in patients who were refractory to the drug's "relative" Revlimid® (lenalidomide) and to Velcade® (bortezomib). This promising medicine is currently further evaluated in combination therapy (e.g. with cyclophosphamide) and expectations are high!

- Elotuzumab

The name of this monoclonal antibody sounds also familiar since last year's ASH. In San Diego, Dr. Lonial provided an update of a phase 2 trial where elotuzumab is combined with lenalidomide and low dose dexamethasone. This promising combination gave excellent responses (> 80%) in relapsed/refractory patients.

- Vorinostat

Dr. Siegel gave an update of the Vantage 95 study (see report ASH 2010). This study evaluates vorinostat (Zolinza®), a histone deacetylase or HDAC inhibitor, combined with bortezomib (Velcade®) as a salvage therapy for patients who are refractory to bortezomib and IMiDs. Dexamethasone was added if necessary. At least a partial response was seen in 11% of these heavily pretreated patients.

Dr. Dimopoulos assessed the effects of the same cocktail (vorinostat-bortezomib) in a Phase 3 study (Vantage 88) in relapsed/refractory patients. Patients in the vorinostat-bortezomib arm had an improved PFS, compared to their peers who received only bortezomib.

- Panobinostat

There is more hopeful news for patients whose disease became resistant to bortezomib! Dr. Richardson explained the results of the Phase 2 Panorama trial where bortezomib was given with another histone deacetylase (HDAC) inhibitor: panobinostat. Also dexamethasone was added and the combination gave encouraging response rates with manageable toxicity in patients with very advanced disease and who were refractory to bortezomib.

- Bendamustine

In a phase 1/2 study, bendamustine (a medicine that has been used for a long time in East European countries) has been tested in a new combination with Revlimid® and dexamethasone in relapsed/refractory myeloma patients. Dr. Lentzsch explained that this three-drug regimen was a safe and well-tolerated treatment in this patient group up to 80 years of age. She noted that patients responded quickly to the treatment and that efficacy was also seen in patients who have relapsed under Revlimid®.

4. Update about Smoldering Multiple Myeloma (SMM)

By reading this report, the smoldering patients among us might think that the attention of the scientists at the ASH congress was only on MM patients who need active treatment.

The young and active Spanish researcher Dr. Mateos proved that this was not the case as she presented a very interesting study in this setting. In her trial, 119 patients with asymptomatic multiple myeloma, who were considered to be at high risk for progression (based on their levels of the monoclonal proteins in the serum and the concentration of plasma cells in the bone marrow) were included.

As we know, the classic clinical approach in those patients is watchful waiting and to start treatment when the SMM evolves to symptomatic MM.

The smoldering patients were randomized to a “therapeutic abstention group” (no treatment), consisting of 62 patients or a group of 57 patients who were treated with induction therapy of lenalidomide (Revlimid®) 25mg and dexamethasone (9 cycles) followed by lenalidomide 10mg maintenance for up to two years.

In both arms, patients were observed for progression to active disease.

In the abstention arm, 59% of the patients progressed after a median of 25 months. In the treated group of SMM patients, 16% developed active disease but 5 of these progressions occurred after patients stopped therapy early. There was a trend to better OS observed in the group of treated patients, although this needs further confirmation.

The side effect profile of the treatment was acceptable. These side effects (mostly skin rash, diarrhea and infections) were generally mild (grade 1 or 2) and it needs to be said that similar adverse events were observed in the patients who were not treated! For the time being, no increased risk of SPMs is observed.

These results suggest that early treatment of SMM in high-risk patients has the potential to prevent damage before it occurs while waiting for disease progression. Moreover, biological progressions (not yet giving symptoms) occurring under maintenance have remained controlled over a prolonged period of time.

The statistical power of this study is quite strong but we need to see the results replicated in other independent studies. Further validation of these findings might influence the approach doctors have towards high-risk SMM patients!

Although slightly tired after this busy ASH meeting, I was not able to catch sleep on the plane during the long night flight home.

While observing the black night through the plane's window, I discovered the first hesitant rays of light from the upcoming sun at the far horizon. Fascinated by this beautiful spectacle of nature, I saw how the early morning sky progressively became illuminated by the brilliant colors of the sunrise, framing the dark earth. That inspirational picture of a new day was a perfect wrap-up of my trip to the ASH meeting. As the new daylight started to outshine the darkness of the black night, I looked back at all the news I had witnessed at the ASH meeting. Lots of good news that progressively, as the sunrise, start to outshine the dark prognosis that once accompanied the diagnosis of multiple myeloma...A new day and a new future definitely break through for myeloma patients!

Greetje Goossens

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