

Report of the 52nd ASH meeting in Orlando, USA

Who says Orlando, Florida says theme and water parks: Walt Disney, Epcot, Universal Studios, Seaworld... Well...mostly, but not always!
The 1st week of December 2010, we had completely different activities in mind when going to Orlando. We went to this sunny state in order to attend the 52nd Annual Meeting of the American Society of Hematology (ASH).

From December 4th until December 7th, approximately 23.000 people visited the huge Orange County Convention Center. The crowd consisted of a fine selection of scientists, researchers, hematologists, various health care professionals, delegates of pharmaceutical industry and patient representatives.

Our organization EMP, *European Myeloma Platform*, was represented by 3 of our colleagues: Ruth Bähler (EMP boardmember and chairperson of the Swiss group MKgS, *Myelom Kontaktgruppe Schweiz*), Antoine Jottrand (EMP collaborator and web-manager) and Greetje Goossens (EMP counselor and boardmember of the Belgian CMP, *Contactgroep Myeloom Patiënten*).

The yearly ASH meeting is the place of pilgrimage for specialists in the field of hematology. At this high quality meeting, special lectures, scientific and educational programs update the audience on the progress made in the field of hematology. Results of research and clinical trials are published and the program focuses on new developments in treatments. Moreover, new practice strategies for patient management are discussed in the different specialized areas of hematology.

Of course, our points of interest were the sessions on Multiple Myeloma.

During the presentations, the efficacy of the novel agents¹ - thalidomide, lenalidomide (Revlimid®) and bortezomib (Velcade®) - in the treatment of MM patients was confirmed and they are now used in a broad spectrum of patients. A lot of attention was on the benefit of maintenance treatment with these agents.

A whole new generation of anti-myeloma medicines is on the way and the first results of clinical trials show their efficacy. With extended survival, it is increasingly important to pay attention to the quality of life of the MM patients and this topic was also addressed in several presentations. And finally some interesting news on the use of bisphosphonates as well as an update on the management of MGUS and smoldering myeloma.

Now, I would like to invite you to sit down, make yourself comfortable and prepare for the news at ASH 2010!

1. First-line Treatment of transplant eligible MM patients:

Some of the studies presented in this report are mentioned under heading 1.1 (Induction therapy) as well as under heading 1.2 (Consolidation and Maintenance therapy). This because every phase of the treatments has particular characteristics and observations which are worth to explore separately.

1.1 Induction therapy before Autologous Stem Cell Transplantation (ASCT):

Already at last year's ASH conference in New Orleans (2009), a lot of attention was on the new concept of induction treatment before ASCT, where the novel agents (and combinations of these) replace the traditional VAD therapy. The presentations at this year meeting confirmed these findings with more data.

Some additional studies worth to mention in this setting:

- The HOVON 65/GMMG-HD4 study (Sonneveld et al).

The goal of this study was to evaluate the efficacy of bortezomib (Velcade®) during induction and maintenance on progression free survival (PFS) in newly diagnosed transplant eligible patients (see also 1.2.1).

Half of the patients were induced with PAD (bortezomib or proteasome inhibitor, doxorubicin or Adriamycin®, dexamethasone) and received bortezomib maintenance for 2 years after the

¹ probably the term "novel agents" is soon not suitable anymore as in the meantime we know these drugs quite well and a whole generation of new drugs point at the horizon

transplantation. The other half received the traditional VAD (vincristine, Adriamycin® and dexamethasone) induction regimen prior to ASCT and they were subsequently put on thalidomide maintenance for 2 years after transplantation. Bortezomib induction proved to be more efficient in terms of response rates, is well tolerated and is especially useful in patients with renal insufficiency and/or unfavorable cytogenetics.

- VTD versus TD (GIMEMA²-study)

The Italian group of Dr. Cavo showed the superiority of VTD (bortezomib, thalidomide, dexamethasone) compared to TD (thalidomide and dexamethasone) in obtaining complete or near complete response both before and after tandem ASCT (see also 1.2.1).

- TD versus VTD versus VBMCP/VBAD/B

A Spanish Phase 3 PETHEMA/GEM³ Study went a step further than the Italian study and added a third arm. The Spanish scientists compared three induction therapy regimens prior to ASCT: TD (thalidomide and dexamethasone), VTD (bortezomib, thalidomide and dexamethasone) and a rather complicated multi-step combination therapy: vincristine , carmustine or BCNU, cyclophosphamide, melphalan, prednisone, dexamethasone, and bortezomib that goes by the acronym “VBMCP/VBAD/B.”

Induction with VTD resulted in significantly higher complete response (CR) rates than the other arms and this observation was also seen in patients with high-risk cytogenetics. The post-ASCT CR rate was also significantly higher with VTD than with TD and there was a similar trend when compared with VBMCP/VBAD/B. Finally, VTD resulted in a significantly longer PFS. However, longer follow-up is required to establish whether or not VTD will overcome the poor prognosis of patients with high-risk cytogenetics.

- Combination lenalidomide and bortezomib

Combining lenalidomide with bortezomib seems a highly effective and powerful induction regimen, with an acceptable toxicity profile. Studies on VRD (bortezomib, lenalidomide, dexamethasone) are ongoing and we look forward to further results on overall survival as well as information on the characteristics of possible relapses, which are feared by some to be possibly more resistant.

1.2 Consolidation and Maintenance therapy after ASCT: the HOT topic of the ASH 2010!

High dose therapy and ASCT is an efficient therapy for the younger and fitter myeloma patients but the large majority of these patients unfortunately relapse. At this meeting, a lot of attention was on the role of “maintenance” therapy and the possible benefits of post-treatment maintenance with as goal to extend remission and overall survival.

1.2.1 Maintenance therapy with **bortezomib** (Velcade®) in patients, eligible for ASCT

- HOVON 65/GMMG-HD4 study

This important trial (see also 1.1) comparing PAD before transplantation followed by bortezomib maintenance with VAD before transplantation and thalidomide maintenance, showed a significant prolongation of the PFS (progression free survival) and OS (overall survival) in favor of the bortezomib arm.

Response, PFS and OS were better in the bortezomib treated patients. Moreover, maintenance therapy with bortezomib was better tolerated, compared to thalidomide allowing the bortezomib treated patients to adhere better to their maintenance therapy. As said before, bortezomib based regimens are the treatment of choice in patients with renal problems and the medicine seems to overcome unfavorable cytogenetics.

- VTD versus VT (Cavo et al)

² GIMEMA: Gruppo Italiano Malattie e Matologiche dell'Adulto (Italian Group for Adult Hematologic Diseases)

³ PETHEMA: Programa para el Tratamiento de Hemopatías Malignas (Program for the treatment of hematological malignancies, Spain)
GEM: Grupo Español Mieloma (Spanish Myeloma Group)

The Italian study (see also 1.1) provided additional information on bortezomib in the maintenance setting. In this phase 3 study, the newly diagnosed patients received consolidation therapy with the same regimen as their induction therapy, either bortezomib, thalidomide, dexamethasone (VTD) or thalidomide, dexamethasone (TD), followed by maintenance with dexamethasone.

Consolidation with VTD increased complete and near-complete responses. PFS was superior in the VTD group, compared to TD. Additionally, here also bortezomib overcame the poor prognosis of patients with the chromosomal abnormalities e.g. t(4;14).

In this study, we also observe a tendency (although statistically not significant) of improved OS in the VTD-arm.

Unlike the before mentioned HOVON 65/GMMG-HD4 study, patients in the thalidomide arm of the Italian study did not suffer from greater toxicity (compared to their fellow patients on bortezomib), leading to discontinuation of the maintenance treatment.

1.2.2 Maintenance therapy with **lenalidomide** (Revlimid®) in patients, eligible for ASCT.

There are 2 exciting studies, providing us with useful data on the use of lenalidomide after transplantation.

- The IFM-study (IFM 2005-2 study, Attal et al)

In this French IFM⁴-study, MM patients under 65 years received two consolidation cycles with lenalidomide after high-dose therapy and stem cell transplantation. Subsequently, the patients were randomized to receive long-term maintenance (until relapse) with low-dose lenalidomide or placebo maintenance treatment.

Patients who received the lenalidomide maintenance therapy had significantly better results from their treatments and had longer PFS compared to their fellow patients who did not follow any maintenance therapy after ASCT (median PFS was 42 months with lenalidomide and 24 months with placebo). However, up to now no difference in the OS rates between the 2 patients groups could be observed and longer follow-up is needed to appreciate the impact of lenalidomide on OS.

This study supports the use of lenalidomide as maintenance therapy after ASCT but patients on long-term lenalidomide maintenance have to be aware that they can suffer from some side effects, most commonly low white blood counts.

For completeness, we mention here that in a small group of patients receiving lenalidomide maintenance therapy, a Second Primary Malignancy (SPM: a new (other) primary cancer developing in a person with a history of cancer) was diagnosed. Although the number of SPMs was low, it seemed slightly higher in the lenalidomide group than in the placebo group (20 SPMs in 306 patients in the lenalidomide group and 3 SPMs in 302 patients in the placebo group). This signal should certainly be further confirmed and therefore this is very well followed. We emphasise that this signal was only seen in study context (long-term maintenance therapy with lenalidomide after transplantation and the use of lenalidomide in combination with melphalan-prednisone in patients ineligible for a transplant, see Section 2: study MP vs RMP vs RMP-R). To date, no association is demonstrated between the use of lenalidomide and the occurrence of SPMs when the drug is used before stem cell transplantation or in relapsed/refractory disease (and thus no link between SPMs and the medicine is seen in the current approved treatments with lenalidomide in Europe).

- The CALGB⁵ group study (CALGB 100104)

This phase 3 study is in fact the American counterpart of the above mentioned IFM-study as it also looked at the use of lenalidomide maintenance therapy versus placebo after an ASCT.

The preliminary results of this study showed end 2009 that lenalidomide maintenance prolonged significantly the PFS and as a result, the study was unblinded in mid-2010. As a consequence, the patients who were originally on placebo were also able to receive lenalidomide as maintenance.

The follow-up results, presented at this ASH meeting showed that lenalidomide maintenance therapy improves the response and prolonged the PFS (progression free survival) compared to transplantation alone (time to progression was 42,3 months in the lenalidomide arm and 21,8 months in the placebo group).

⁴ IFM: Intergroupe Francophone du Myélome

⁵ CALGB: The Cancer and Leukemia Group B

This benefit was also observed in patients who achieved a complete response after initial treatment. These findings demonstrate the importance of maintenance therapy for MM patients, even if the patient achieves a good response after transplantation; an observation also made in the IFM 2005-02 study.

The study was not able to draw strong conclusions of the impact of lenalidomide maintenance therapy on OS. This might be due to the crossover of patients to lenalidomide maintenance at first interim analysis.

It has to be said that lenalidomide patients were more likely to suffer from side effects although there were considered manageable.

Here also, good monitoring of patients is advised because of the possible occurrence of a Second Primary Malignancy (SPM) in a very small group of people in this study context (19 SPMs in 231 patients in the lenalidomide arm and 5 SPMs in 229 patients in the placebo arm).

1.2.3 Maintenance with **thalidomide** in MM patients, eligible for ASCT

Dr. Morgan presented a study where maintenance treatment with thalidomide has been observed in a large group of patients, consisting of transplant candidates and patients, not eligible for transplantation (for more information about this study see point 2.)

2. Treatment of MM patients, not eligible for transplantation

The role of the novel agents in the treatment of non-transplant candidates is well recognized. This year at ASH, focus was also on maintenance therapy in this patient group.

- Study comparing MP versus RMP versus RMP-R (Palumbo et al)

A Phase 3 study evaluated the efficacy and safety of lenalidomide, in combination with melphalan and prednisone in newly diagnosed patients above 65 year and studied the continuous use of lenalidomide versus fixed duration regimens.

Patients were randomized to receive MP (melphalan/prednisone), MPR (melphalan, prednisone and lenalidomide) or MPR-R (melphalan, prednisone and lenalidomide, followed by lenalidomide maintenance).

Results showed that responses were more rapid and better with MPR-R than MP. A comparison of the three different regimens showed that the lenalidomide maintenance regimen (MPR-R) had a longer PFS than the two other regimens. The benefit of lenalidomide maintenance therapy is recognized by the scientists but some physicians still had some doubts about the advantage of using lenalidomide upfront in elderly patients.

The backside of this efficient treatment are the side effects (mainly low blood cell counts), mostly occurring during the MPR phase of the treatment (so before the start of the maintenance therapy) and in patients above 75y of age. Although, these side effects are manageable for the many patients, more patients in the MPR-R arm (compared to their fellow patients in the MP arm) discontinued therapy because of the treatment related toxicity.

Prof. Palumbo suggested a good follow-up of the patients because of a possible occurrence of a SPM in a small group of patients (17 SPMs in 302 patients in the MPR and MPR-R groups and 5 SPMs in 153 patients in the MP group).

- Study about thalidomide maintenance

Patients involved in the study were non-transplant eligible patients as well as transplant candidates and the following observation applies to both groups. We have to note that, because of the tolerability profile, the average thalidomide maintenance period in this study was rather short (average of 7 months).

The observations of Dr. Morgan and his team were that patients receiving thalidomide maintenance therapy stayed significantly longer in remission during the first 2 years, compared to patients who had not received maintenance therapy. Despite this initial longer remission period, thalidomide maintenance did not seem to impact overall survival (the benefit was lost by 5 years except in a small sub-group of patients).

Dr. Morgan suggested that thalidomide maintenance treatment is useful but that the average maintenance period was too short to fully confirm its effectiveness. He explained that the clinical impact of maintenance would be improved if patients could remain on therapy for longer, suggesting that the use of other agents such as lenalidomide, with better tolerability profiles, may produce better results.

- New therapies

Many new medicines with promising efficacy in the elderly or non-transplant eligible patient as well as in patients with relapsed disease are emerging at the nearby horizon. More about these treatments in point 3.

3. Treatment of relapsed and refractory MM: new effective medicines come within reach!

As has been described above, treatment for MM has dramatically changed over the past decennium. However, recurrent disease relapse as well as drug resistance remains a major challenge in the treatment of MM, prompting the development of additional targeted agents and combination regimens. Exciting news about a new generation of anti-myeloma medicines was presented at ASH. These medicines have promising activity in relapsed/refractory MM and include:

- Carfilzomib: a new proteasome inhibitor, that works similarly to Velcade® (bortezomib)

We learn from several studies (Ravi Vij et al, Andrzej J. Jakubowiak et al, Sundar Jagannath et al) that the drug seems to overcome unfavorable prognosis as patients with chromosomal abnormalities had a good response to this new drug.

Moreover, patients were less likely to suffer from peripheral neuropathy (a debilitating side-effect common in treatment with bortezomib) and other adverse reactions, although pneumonia occurred in some patients. Long-term results showed that patients seemed to tolerate carfilzomib well and were able to adhere to extended treatment (60% of patients are still in treatment after 11 months and 30% have been treated for over 18 months).

- Pomalidomide: a third generation IMiD (immunomodulatory drug)

We are already familiar with 2 immunomodulatory drugs: thalidomide and lenalidomide. Succession is guaranteed: the new kid is pomalidomide!

Results of several studies (among them the IFM 2009-02 -study) on different administration schedules of pomalidomide with low dose dexamethasone show that pom/dex is remarkably active in patients who are relapsed or refractory after prior treatments including lenalidomide, thalidomide and bortezomib.

The majority of patients have not yet progressed. These studies confirm therapeutic benefit for pom/dex in patients relapsing after other novel therapies.

- Vorinostat

We learned more about the activity of this drug in the treatment of MM. Vorinostat is a histone deacetylase or HDAC inhibitor that is already approved for a certain type of lymphoma.

Dr. Paul Richardson presented the results of a phase I study where vorinostat was combined with lenalidomide and dexamethasone as therapy for patients with relapsed or relapsed/refractory MM. The first findings show that the medicine has a good tolerability (most common side effects were low blood cell counts, fatigue and diarrhea and were reported to be mild or moderate) and a promising activity in a heavily pretreated population. Further evaluation of this regimen is planned in future trials.

Interim results of a Phase 2 study (now entering Phase 3), were presented by Dr. Siegel (update on the Vantage Study Program).

In this study, vorinostat is combined with bortezomib in patients with relapsed or relapsed/refractory MM. The interim results suggest that combined vorinostat and bortezomib may have clinical activity in patients who are refractory to bortezomib (so the combination seems to overcome the initial resistance to bortezomib!) and IMiDs, and who are ineligible for other regimens.

- Panobinostat

Research of Offidani et al shows that half of the relapsed/refractory patients involved in the trial respond to the treatment with a combination of panobinostat (a HDAC inhibitor), melphalan, prednisone and thalidomide (17% achieving a very good partial response). However, the dose of panobinostat had to be reduced as the initial dose was associated with severe side effects. The toxicity profile improved with lower doses although side effects like low white blood cell counts remain a challenge, prompting for further investigation on different dosing schedules.

- Elotuzumab

This monoclonal antibody was being tested in a Phase 1 trial (Lonial et al) in combination with lenalidomide and low-dose dexamethasone in relapsed/refractory patients who had received multiple prior therapies.

This combination was generally well tolerated and showed encouraging overall response rates in this patient population. A larger phase 2 study is ongoing to confirm the rate and durability of the responses observed in this Phase 1 trial.

Other new agents with promising activities are being tested in clinical trials. Names to remember are Lorvotuzumab mertansine (IMGN901) and Perifosine.

4. Different administration schedules and administration forms of known treatments can improve the Quality of Life (QoL) of MM patients!

As we have seen, the improved treatments extend considerably the life expectancy in the majority of MM patients. Consequently, the QoL during and after the treatment and the management of side-effects becomes an increasingly important aspect that has to be taken into account when considering treatment options. Different administration schedules and forms have been studied with as goal to lessen the burden of treatment, while preserving full effectiveness.

- Subcutaneous administration of bortezomib (Velcade®)

A randomized IFM Phase 3 clinical trial compared subcutaneous and intravenous administration of bortezomib in patients with relapsed MM. This new subcutaneous administration demonstrates efficacy consistent with the intravenous administration of bortezomib. Moreover, an important finding of this study is the dramatic reduction in peripheral neuropathy with the subcutaneous administration, making it an attractive route of administration.

- *Velcade® “light” – schedule*

Most of us are familiar with the a 2x/week administration of bortezomib for 2 weeks, placed in a 3-week cycle. Indeed, this is an effective treatment schedule, but unfortunately many patients suffer from associated side-effects, mostly peripheral neuropathy.

The team of Dr. Munshi studied a once a week administration (during 4 weeks in a 5 week-cycle) of bortezomib with dexamethasone instead of the usual bi-weekly administration, in older and/or less fit previously untreated MM patients. The patients received a maximum of six cycles.

Further studies will be needed to confirm but initial findings are that a once a week schedule of bortezomib is equally effective and better tolerated (there were no reports of peripheral neuropathy) in this group of patients than the twice a week schedule, offering an alternative anti-myeloma treatment with less side-effects for patients who do not tolerate the existing bi-weekly schedule.

These findings have also been confirmed in several other studies.

- *Dexamethasone “light”*

Study comparing lenalidomide + high dose dexamethasone (RD) with lenalidomide + low dose dexamethasone (Rd)

We learned already from the previously published ECOG trial (2009) that patients in the Rd arms had a longer OS. At this years' ASH, further analysis of the trial data provided us with more interesting information. The finding of a prolonged OS in the Rd arm is irrespective of the age of the patients.

Moreover, older patients treated with RD showed a more rapid disease progression than younger patients in the same arm. Younger patients in the RD arm showed initially a better response than their fellow patients in the Rd arms, but ultimately this did not translate into better PFS or OS.

We may conclude from these results that lenalidomide should be combined with low dose dexamethasone as a standard of care for all newly diagnosed patients who receive lenalidomide, regardless of their age.

5. Update on Zometa.

Dr. Gareth Morgan presented the results of a large Phase 3 clinical trial, showing that Zometa increases overall and progression free survival rates among MM patients, compared to Bonefos.

Zometa (zoledronic acid) and Bonefos (clodronic acid, mostly used in the UK, Italy and Canada) are both bisphosphonates and are used to reduce bone loss and fractures in MM patients. Zometa also seemed to be more effective in preventing bone loss and fractures.

According to Dr. Morgan, the increase in overall survival, observed in the Zometa patients can be explained by the anti-cancer effects of the drug, rather than by the decrease in skeletal-related events.

Worth to mention is that after bisphosphonate treatment, all patients in the study had the option of receiving maintenance treatment with thalidomide. It was observed that patients who opted for thalidomide had a significant higher percentage of CR (complete remission) and VGPR (very good partial response) than the patients who did not receive thalidomide.

6. Update on management of patients with MGUS and Smoldering Myeloma (SMM).

A study published by Dr. Landgren shows that multiple myeloma is always preceded by MGUS⁶ (although this condition is often not diagnosed).

MGUS possibly progresses to SMM, which can further evolve to MM. Generally spoken, the average rate of progression from MGUS to MM (or a related blood disease) is 1%/year.

SMM has a higher rate of progression. A smoldering myeloma diagnosis is made when serum monoclonal protein levels (IgG or IgA) are 30 g/l or greater and the proportion of plasma cells in the bone marrow is 10 percent or greater, but there is no associated organ damage.

The first 5 years following SMM diagnosis represent a risk of 10% per year of progression to MM.

After the initial 5 years, the risk of progression drops to 3% per year for the next 5 years. After that, the risk of evolution to MM drops further to a low rate of 1% per year.

Evidence-based recommendations for MGUS and SMM state that treatment with cytotoxic agents should be delayed until the disease becomes progressive with identification of CRAB criteria⁷.

However, several clinical trials are ongoing to determine if early treatment of SMM can prevent or delay progression to symptomatic MM.

Preliminary results from an ongoing Phase 3 study (Mateos et al) in patients with high-risk SMM show us that treatment with lenalidomide and dexamethasone induced complete responses and delayed the time to progression, compared with therapeutic abstention in SMM.

Nevertheless, more research is necessary as these results need further long-term confirmation. Some scientists also wonder if early treatment could lead to more aggressive disease at relapse.

For the time being, SMM patients should only be treated in the context of a clinical trial.

For me, being a MM patient, it was again a unique experience to attend the ASH meeting, this time celebrating its 52nd anniversary. I had the privilege to listen to the knowledge of the researchers, to observe with delight the huge motivation and commitment of the MM specialists and to absorb their contagious excitement about the advances made in the treatment of our disease.

It is not only my duty, but first of all my great pleasure to share the exciting ASH news with my fellow patients and I tried to do my best to resume the most important news items, likely to have a fast impact on the management of our condition. Despite the difficult and challenging disease MM-patients and their families are confronted with, I hope this report will bring them a piece of hope, trust and confidence when looking at the future.

Greetje Goossens

⁶ MGUS: Monoclonal gammopathy of undetermined significance.

All 3 criteria must be met:

- Serum monoclonal protein < 3g/dL
- Clonal bone marrow plasma cells < 10%
- No end-organ damage (such as CRAB criteria: see footnote nb.7)

⁷ CRAB criteria: evidence of end-organ damage, due to the underlying plasma cell proliferative disorder:

Calcium elevation: serum calcium \geq 11.5 mg/dL or

Renal insufficiency: serum creatinine > 2 mg/dL

Anemia: haemoglobin 2g/dL below the lower limit of normal or haemoglobin <10g/dL.

Bone lesions: lytic lesions, severe osteopenia or pathologic fractures