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REVIEW – CLINICAL ONCOLOGY

Meeting report of the 5th Heidelberg Myeloma Workshop: current status and developments in diagnosis and therapy of multiple myeloma

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Abstract
Purpose The 5th Heidelberg Myeloma Workshop was held on April 24 and 25, 2015, in the lecture hall of the department of internal medicine of the University Hospital of Heidelberg, Germany.
Methods and Results Main topics of the meeting were (1) new insights into biology of plasma cell diseases, (2) familial risk in multiple myeloma (MM), (3) diagnosis and prognostic factors in MM and early plasma cell diseases, (4) frontline therapy in transplant-eligible and (5) transplant-ineligible patients as well as (6) treatment of relapsed disease.
Conclusion Better understanding of disease biology led to tremendous changes in the treatment of multiple myeloma in recent years and were reported during the meeting.

Keywords Multiple myeloma · Clonal heterogeneity · Autologous · Stem cell · Transplantation · Imaging · Bortezomib · Lenalidomide · Carfilzomib · Pomalidomide · Elotuzumab · Daratumumab

Biology of multiple myeloma

Multiple myeloma (MM) is a genetically heterogeneous disease and can be classified based on karyotyping as hyperdiploid and non-hyperdiploid. While hyperdiploid MM is characterized by gain of odd chromosomes (3, 5, 7, 9, 11, 15, 19 and 21), non-hyperploid MM cells harbor translocations in the heavy chain locus on 14q32 with one of several partners [e.g., t(4;14) and t(14;16)]. As demonstrated by Gareth Morgan and Niels Weinhold from Little Rock, another layer of complexity is added by whole genome sequencing showing a widespread range of different genomic mutations in MM. Genomic diversity is not only a phenomenon observed when looking at probes from different MM patients, but is also observed in single patients, since different chromosomal aberrations or genomic mutations can be present in several subclones at the same time. Recent data from next generation sequencing (NGS) demonstrated that clonal heterogeneity is present in patients with early plasma cell disease and evolves during the progression to symptomatic MM. Such clonal evolution is also observed during progression of the disease, leading ultimately to refractory MM or plasma cell leukemia. The process of clonal evolution is favored by increasing genomic instability. An enzyme involved in maintenance of chromosomal stability is the DNA unwinding helicase RECQ1. Jerome Moreaux from Montpellier demonstrated that RECQ1 expression is correlated to adverse outcome in MM and could be a surrogate for drug resistance in MM, bridging the gap from clonal evolution and disease biology to clinical outcome and potential therapeutic targeting.

Familial risk in multiple myeloma

Based on the analysis from the Swedish Family-Cancer Database, relatives of patients with MM have a twofold to threefold increased risk of developing MM. The underlying mechanisms of increased familial risk in MM remained

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unexplored for years. Recent genome-wide association studies (GWAS) performed as German–UK collaboration project identified 7 risk loci for MM. Expression quantitative trait loci (eQTL) generated to analyze functional basis of the identified single nucleotide polymorphisms (SNP) showed allele-specific regulation of the MYC-interacting gene CDCA7L by rs4487645 at 7p15.3. The data presented by Kari Hemminki from the German Cancer Research Center, Heidelberg, showed for the first time a connection between familial risk and biology of MM.

Diagnosis and prognostic factors in multiple myeloma and early plasma cell disease

Previous studies showed that symptomatic MM is consistently preceded by a phase in which the patient experiences now symptoms but has evidence for monoclonal protein in serum or urine and a bone marrow infiltration by clonal plasma cells. Previously, several studies tried to identify risk factors for progression of monoclonal gammopathy of undetermined significance (MGUS) and smoldering MM (SMM) into symptomatic disease. Most of these risk factors are surrogates for tumor load, e.g., pathologic free light chain (FLC) ratio (involved/uninvolved >100), presence of monoclonal bone marrow plasma cells (BMPC) > 60 % or presence of more than 1 focal lesion in MRI. Also cytogenetic abnormalities like del17p, t(4;14) and gain1q21 are associated with a higher risk of progression from SMM to MM. While until 2014 patients with asymptomatic disease were not considered candidates for systemic chemotherapy, a landmark study by Mateos et al. changed the landscape for patients with high-risk SMM. For the first time, early treatment initiation with lenalidomide/dexamethasone prolonged progression-free survival (PFS) and most importantly overall survival (OS) of patients with high-risk SMM. These findings were summarized by Ola Landgren from the Memorial Sloan Kettering Cancer Center, who also presented impressive data on the three-drug combination treatment with carfilzomib/lenalidomide/dexamethasone in patients with high-risk SMM. High rates of complete remission achieved by early aggressive treatment might lead the way to long-term disease control and probably cure of MM. The current developments in high-risk SMM are also appreciated in the updated International Myeloma Working Group (IMWG) criteria for the diagnosis of MM that were discussed during the meeting. Beyond the presence of CRAB criteria, patients with BMPC > 60 %, FLC ratio > 100 or more than 1 MRI focal lesion should be considered candidates for systemic therapy, since they inevitably develop CRAB criteria. It was furthermore discussed during the meeting by Stefan Delorme and Jens Hillengass from the University of Heidelberg and the German Cancer Research Center, that myeloma bone disease should no longer be examined with plain films, since whole body MRI and CT exhibit higher sensitivity and specificity for detecting bone marrow lesions and osteolyses.

Several strategies have evolved for risk stratification in symptomatic MM. Risk scores based on gene expression profiling (GEP) reliably stratify patients with respect to outcome. Dirk Hose from Heidelberg demonstrated that GEP can be preformed in clinical routine within 4–6 weeks in the large multicenter GMMG-MM5 trial (78 % of 504 enrolled patients) at reasonable costs (600€/patient). However, GEP-based risk assessment remains challenging, since several scores are currently available (e.g., UAMS 70 gene score and IFM 15 gene score). Furthermore, Philippe Moreau from the University of Nantes emphasized that although risk-adapted therapies are supported by the community, so far no clinical trial evaluated prospectively such a tailored approach.

Another approach to risk-adapted therapy is to modify treatment according to depth of remission as surrogate for OS. Brian Durie from the International Myeloma Foundation (IMF, Los Angeles) emphasized the detection of minimal residual disease (MRD) as link between long-term remission and even cure of MM in his keynote lecture. Bruno Paiva from the University of Navarra presented recent data underlining that MRD negativity is a potential biomarker to evaluate early treatment efficacy and might help to decide whether treatment should be prolonged or stopped. MRD assessment with a target cut-off 10^{-5} as surrogate for OS offers the opportunity to compare early results from clinical trials, probably without the need for long-term follow-up. Which method should be used for MRD detection needs to be investigated in the future. Among different methods like NGS, allele-specific oligonucleotide-based polymerase chain reaction (ASO-PCR) of immunoglobulin genes or sensitive imaging modalities like PET/CT, multiparametric flow cytometry (MFC) is currently the most established method. MFC performed on fresh bone marrow samples with at least 8 markers exhibits a high sensitivity (-10^{-6}), can be acquired within 2–3 h at reasonable costs per probe (ca. 250€) and is currently standardized by the EuroFlow consortium and the Black Swan research initiative. As summary of his talk on MRD, Bruno Paiva coined the phrase that state of the art therapy should go along with state of the art diagnosis and monitoring.

Treatment of transplant-eligible patients

Pieter Sonneveld from the Erasmus Medical Center Cancer Institute in Rotterdam presented recent data on upfront treatment in transplant-eligible patients in his keynote

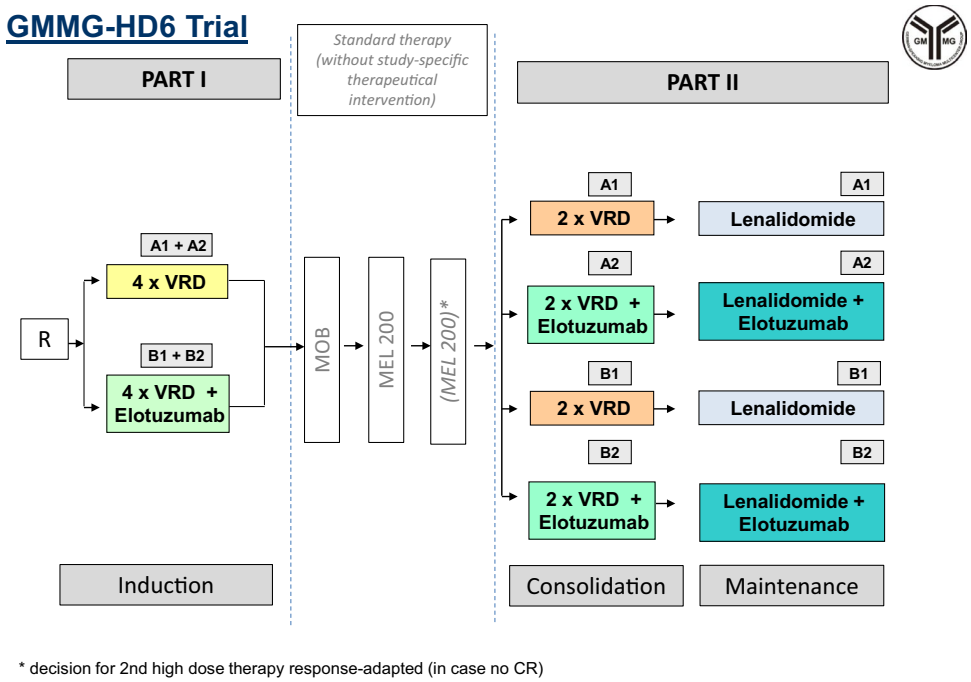


Fig. 1 Flowchart of the GMMG HD6 trial. Patients are randomized into 4 arms: Treatment is defined by VRD (bortezomib/lenalidomide/dexamethasone) versus VRD plus elotuzumab induction therapy; high-dose melphalan followed by autologous stem cell transplantation as well as consolidation therapy with VRD or VRD + elotuzumab and maintenance therapies with lenalidomide or lenalidomide + elotuzumab

lecture. Incorporation of immunomodulatory drugs (IMiDs) and proteasome inhibitors (PI) before and after high-dose therapy increased rates of CR up to 60 %. Bortezomib-based induction therapy prolongs PFS and OS compared to conventional chemotherapy. Furthermore, Christoph Scheid from the University of Cologne summarized updated results from the GMMG HD4/HOVON65 trial that demonstrated for the first time that bortezomib before and after autologous stem cell transplantation (ASCT) is able to overcome adverse effects of renal impairment and del17p at baseline. However, combination treatments of second-generation IMiDs and PIs without ASCT like carfilzomib/lenalidomide/dexamethasone (KRd) achieved impressive results in current phase II trials. Therefore, the role of upfront versus delayed ASCT is currently under investigation in 2 large phase III trials from the European Myeloma Network (NCT01208766) and in a joined French/US trial (NCT01208662). Antonio Palumbo from the University of Torino presented results from the recently published phase III trial comparing consolidation therapy with melphalan/prednisone/lenalidomide (MPR) or tandem ASCT after lenalidomide/dexamethasone (Rd) induction therapy. In both arms, patients were randomized after consolidation treatment to lenalidomide maintenance or observation. In this study, patients treated with tandem ASCT and lenalidomide maintenance had the longest PFS and OS. In an open discussion between Niels Abildgaard from the Nordic Myeloma Study Group and Roman Hajek from the University Hospital Brno, it was emphasized that the main goal of maintenance therapy after ASCT should be prolongation of OS and not only PFS without impairment of quality of life at reasonable costs. Therefore, future studies should implement analysis of second-line treatment and PFS-2, defined by the time from randomization to second progression of the disease. Another exciting development is the integration of antibodies into the high-dose therapy concept. In the GMMG HD6 trial that will start recruiting in 2015, the anti-CS1/SLAMF7 antibody elotuzumab will be implemented before and after high-dose therapy (Fig. 1). Hartmut Goldschmidt from the University of Heidelberg and the National Center for Tumor Diseases pointed out that in the HD6 trial the three-drug combination bortezomib, lenalidomide, dexamethasone (VRD) plus long-term treatment with elotuzumab might induce long-term MRD negative remission.

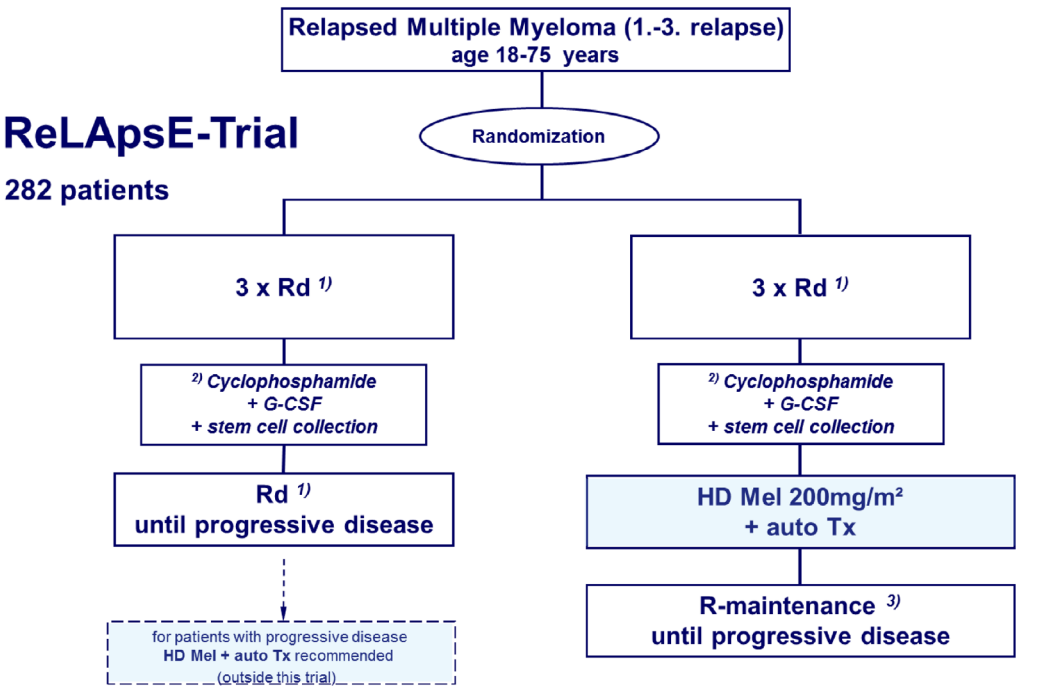
Treatment of transplant-ineligible patients

The landscape for upfront treatment in transplant-ineligible patients changed significantly with the publication of the FIRST trial, the largest trial ever performed in elderly MM patients. Cyrille Hulin from the University Hospital of Nancy presented the respective data showing for the first time that continuous treatment with Rd prolongs PFS compared to fixed treatment with Rd or melphalan/prednisone/thalidomide (MPT) for 18 cycles. The comparison between Rd treatment until progression versus 18 cycles MPT shows a prolongation of OS. These results led to the approval of Rd as frontline treatment in Europe and the USA. Another standard treatment for elderly patients is the combination of bortezomib/melphalan/prednisone (VMP). Results from the GEM2010MAS65 trial investigating sequential versus

alternating treatment with 9 cycles Rd and 9 cycles VMP were presented at last year's ASH meeting and showed no significant differences in PFS and OS. However, compared to the best arms of the VISTA trial (VMP; median PFS 21 months) and FIRST trial (continuous Rd; 25 months), the GEM2010MAS65 trial showed an excellent outcome in both arms (alternating; median PFS 34 months, sequential; median PFS 32 months) so that Cyrille Hulin called the respective treatment "total therapy" for the elderly patient. However, treatment intensity in elderly patients should be adjusted to age, geriatric assessment and comorbidities. Antonio Palumbo presented data indicating that frailty is a major adverse factor for OS. While elderly patients without severe comorbidities should be treated with three-drug combinations, treatment in frail patients should be started with two-drug combinations and switched to three drugs, when patient condition improves upon remission of the disease.

Treatment of relapsed disease

Heinz Ludwig from the Wilhelminenspital in Vienna gave an overview of currently available options for relapsed MM. The first important step in the treatment of relapsed/refractory myeloma (RRMM) is the optimal timing for initiation of therapy. It is important to differentiate between biochemical relapse and symptomatic progression. While patients with an isolated increase in monoclonal protein in serum/urine might not automatically need second-line treatment, patients with symptomatic progression due to hypercalcemia, new osteolyses, renal failure or extramedullary disease need to be treated right away. General considerations before the treatment of RRMM should include the components of first-line treatment, efficacy of first-line treatment (depth and duration of remission, side effects) and current patient status. If a patient for example had not achieved a long-lasting remission after first-line treatment and experienced severe side effects, the treatment strategy should be changed. Patients with deep remission >12 months and no severe side effects after first-line treatment might profit from re-exposition. In general, a second ASCT should be considered in patients who are transplant-eligible and experienced at least 12 months remission after first-line ASCT. In that context, the ongoing GMMG ReLApsE trial compares consolidation treatment with ASCT after Rd re-induction therapy followed



1) Revlimid ® (Lenalidomide) 25mg p.o., day 1-21; Dexamethasone 40mg p.o., day 1, 8, 15, 22
2) stem cell mobilization only if no useable stem cells from earlier mobilization are available
3) Revlimid ® (Lenalidomide) - maintenance 10mg/day
R-Revlimid ® (Lenalidomide), d-Dexamethasone, HD Mel - high dose chemotherapy Melphalan, Auto Tx - autologous stem cell transplantation

Fig. 2 Flowchart of the GMMG ReLApsE trial. Patients are randomized into 2 arms: Treatment is defined by continuous treatment with Rd (lenalidomide/dexamethasone) versus 3 cycles Rd induction therapy followed by autologous stem cell transplantation as well as maintenance therapy with lenalidomide. In both arms, stem cells are harvested after 3 cycles Rd, if no viable stem cells from primary treatment are available

by lenalidomide maintenance therapy with continuous Rd treatment (Fig. 2).

Despite all efforts, most MM patients become refractory to treatment with lenalidomide and bortezomib resulting in a devastating median OS of approximately 9 months. Katja Weisel from the University Hospital of Tübingen presented recently published data on the second-generation IMiD pomalidomide in such double-refractory patients. As shown by the MM003 trial comparing pomalidomide/dexamethasone (PomDex) with high-dose dexamethasone (HiDex), pomalidomide achieved overall response rates (ORR) of approximately 30 % and prolonged median OS (13 months) compared to HiDex (8 months). Most importantly, a subgroup analysis published by Leleu and colleagues provided first evidence that pomalidomide might overcome the adverse impact of t(4;14) in RRMM. Also the second-generation PI carfilzomib is a promising option for double-refractory patients. The recently published ASPIRE trial comparing KRd with Rd treatment in RRMM showed ORR of 87 % and the so far longest PFS ever reported from a phase III in RRMM (26.3 months).

Monoclonal antibodies are another promising option for RRMM. Henk Lokhorst from the University Medical Center Amsterdam presented recent data on daratumumab and SAR650984, both anti-CD38 antibodies with unprecedented single-agent activity in heavily pretreated patients. Both antibodies and the anti-CS1/SLAMF7 antibody elotuzumab are currently under investigation in phase II/III in combination with IMiDs and PIs.

Targeting immune escape mechanisms by blockage of the PD1/PD-L1 axis has shown promising results in malignant melanoma, lung and renal cancer. In his keynote lecture, Kenneth Anderson from the Dana Farber Cancer Center in Boston presented preclinical data showing that immune checkpoint inhibition in combination with IMiDs might also be suitable in MM. However, with increasing complexity of therapeutic options in MM and spatially divergent clonal evolution of the disease, personalizing therapy to overcome resistance should be a future goal. As an example, Marc Raab from the University Hospital of Heidelberg showed how customized MM-specific panel sequencing can be used for therapeutic decision making in the case of targeting the B-Raf V600E mutation with vemurafenib.

Conflict of interest None.

Human and animal rights This work does not include human participants or animals.

Informed consent Informed consent was obtained from all individual participants included in this work.