ASH 2021 Report

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I would like to thank Myeloma UK and Celgene for awarding me a bursary to attend ASH 2021. In light of the ongoing COVID-19 pandemic, ASH 2021 was held as a hybrid event and I attended virtually. This was my first-time attending ASH and I found it to be a really interesting and educational event.

The bursary enabled me to present my work analysing the utility of matrix-assisted laser desorption/ionisation-time of flight mass spectrometry (MALDI-TOF MS) testing for free light chains in the serum of patients treated in the carfilzomib, lenalidomide, cyclophosphamide and dexamethasone arm of the Myeloma XI trial. This study highlighted the utility of being able to specifically and sensitively measure monoclonal free light chains. In this study we found that residual low-level monoclonal light chains are detectable by MALDI-TOF MS in a significant proportion of patients with normal serum free light chain ratios and that the presence of residual monoclonal free light chain in patients undergoing treatment for newly diagnosed symptomatic multiple myeloma is associated with reduced progression free survival (PFS).

Residual Monoclonal Free Light Chain Positivity by Mass Spectrometry Identifies Patients at Increased Risk of Early Relapse Following First-Line Anti-Myeloma Treatment
Giles HV et al
https://doi.org/10.1182/blood-2021-150479

I have summarised some of the oral abstracts that I found particularly interesting below:

Mass Spectrometry Studies

Dr Puig presented the combined results from MALDI-TOF MS and liquid-chromatography mass spectrometry testing (LC-MS) in the GEMMENOS65 trial. In this study, they found that mass spectrometry had a high negative predictive value and that it provided added clinical value. Patients who were in complete response (CR) using standard methodologies but were mass spectrometry positive had shorter PFS compared to mass spectrometry negative patients. However, there were discordances predominantly due to mass spectrometry positive cases that were minimal residual disease (MRD) negative by next generation flow cytometry. Further results from quantitative analyses are awaited to help us better understand these results and determine how many of the flow cytometry negative mass spectrometry positive cases may have been false positives due to long immunoglobulin half-life versus how many may have been due to false negative bone marrow MRD results due to haemodilute samples or patchy residual disease not involving the bone marrow sampling site in the pelvis.

The impact of the increased sensitivity of MALDI-TOF MS for the identification of monoclonal gammopathy of undetermined significance (MGUS) was explored in the PROMISE study. This study involved screening individuals at increased risk of developing multiple myeloma (Black/African American individuals and first-degree relatives of patients with haematological malignancies) for MGUS using the standard screening panel of serum protein electrophoresis, immunofixation and serum free light chain assessments and also using MALDI-TOF MS. MALDI-TOF MS detected monoclonal proteins in twice as many study participants compared to the standard screening panel. However, the rate of transient paraproteins was much higher in the low-level monoclonal proteins that were only detectable by mass spectrometry (35% persisted on repeat testing) compared to those ≥0.2g/L that were detectable using the standard screening panel (95% persisted on repeat testing). Whilst this study emphasises the high sensitivity of MALDI-TOF MS for the detection of the low-level monoclonal proteins, it highlights the need for more studies to understand the long-term implications of low-level monoclonal proteins initially only detectable by mass spectrometry. There is a need for consensus criteria about what constitutes a diagnosis of MGUS when screening is performed using one of the mass spectrometry-based assays.

Assessment of Treatment Response by Ife, Next Generation Flow Cytometry and Mass Spectrometry Coupled with Liquid Chromatography in the GEM2012MENOS65 Clinical Trial
Puig N et al.
https://doi.org/10.1182/blood-2021-151557

High Prevalence of Monoclonal Gammopathy in a Population at Risk: The First Results of the Promise Study
El-Khoury H et al.
https://doi.org/10.1182/blood-2021-149868

Induction and Maintenance Regimens Incorporating Anti-CD38 Monoclonal Antibodies

Dr Goldschmidt presented the post induction MRD results from the GMMG-HD7 trial, which is comparing isatuximab, bortezomib, lenalidomide and dexamethasone to bortezomib, lenalidomide and dexamethasone in transplant-eligible patients with newly diagnosed multiple myeloma. At the end of induction, the addition of isatuximab to bortezomib, lenalidomide and dexamethasone lead to an increased MRD negativity rate (50.1% v. 35.6%) without a significant increase in adverse effects.

Updated results from post 24 months of maintenance with daratumumab and lenalidomide in the GRIFFIN trial also confirmed the ability of daratumumab in combination with bortezomib, lenalidomide and dexamethasone to induce deep and durable responses in a high proportion of patients. At this 24-month maintenance time point, patients treated with daratumumab in combination with bortezomib, lenalidomide and dexamethasone had higher rates of stringent complete response (66% v. 47.4%, p=0.0096) and MRD negativity (64.4 % v. 30.1%, p<0.0001) compared to those treated with bortezomib, lenalidomide and dexamethasone alone.

Dr Kaiser presented the results of the MUKnine OPTIMUM trial and showed that in patients with ultra-high risk multiple myeloma daratumumab, bortezomib, cyclophosphamide, lenalidomide and dexamethasone is a highly active regimen, which lead to improved outcomes compared to the digital comparator arm from the Myeloma XI trial (18 months PFS 81.7% v. 65.9%). This study was notable for its use of a digital comparator arm using patients from the Myeloma XI trial rather than a traditional control arm.

Addition of Isatuximab to Lenalidomide, Bortezomib and Dexamethasone as Induction Therapy for Newly-Diagnosed, Transplant-Eligible Multiple Myeloma Patients: The Phase III GMMG-HD7 Trial
Goldschmidt H et al.
https://doi.org/10.1182/blood-2021-145097

Daratumumab (DARA) Plus Lenalidomide, Bortezomib, and Dexamethasone (RVd) in Patients (Pts) with Transplant-Eligible Newly Diagnosed Multiple Myeloma (NDMM): Updated Analysis of Griffin after 24 Months of Maintenance
Laubach, JP et al.
https://doi.org/10.1182/blood-2021-149024

Daratumumab, Cyclophosphamide, Bortezomib, Lenalidomide, Dexamethasone (Dara-CVRd), V-Augmented Autologous Stem Cell Transplant (V-ASCT) and Dara-Vrd Consolidation in Ultra-High Risk (UHiR) Newly Diagnosed Myeloma (NDMM) and Primary Plasma Cell Leukemia (pPCL) Compared with Myeloma XI/XI+ Trial Treatment for Uhir MM: The UK Optimum/Muknine Trial
Kaiser MF et al
https://doi.org/10.1182/blood-2021-144990

Prognostic Markers

Refining prognostic tools is an important area of research, particularly as differing maintenance strategies (fixed duration versus continuous until disease progression, single agents versus multiagent and MRD-adapted) and treatment in high-risk smouldering myeloma are being explored in multiple clinical trials. Circulating tumour cells (CTC) are an easily measurable prognostic marker that was highlighted as being able to provide additional prognostic information to the monoclonal protein level and bone marrow plasma cell percentage in patients with smouldering multiple myeloma (hazard ratio 1.61, p=0.015). In this study, CTCs were also an independent prognostic factor in patients with newly diagnosed symptomatic multiple myeloma (hazard ratio 1.43, p=0.003) but the adverse prognostic significance of higher levels of CTCs (≥0.02%) could be abrogated by achieving MRD negativity.

Dr Burgos presented the results of a study in which they found that 5% of patients with high-risk smouldering multiple myeloma according to the Mayo or PETHEMA

criteria, had an MGUS-like phenotype and that these patients had virtually no risk of progression to symptomatic multiple myeloma at five years. The MGUS-like phenotype also had prognostic value in patients with symptomatic multiple myeloma and this study demonstrated that patients with an MGUS-like phenotype can have excellent PFS even in the absence of achieving a complete response (13-year PFS for patients with an MGUS-like phenotype achieving CR and 9 years PFS for patients with an MGUS-like phenotype who achieved less than a CR as their maximum response).

Circulating Tumor Cells (CTCs) in Smoldering and Active Multiple Myeloma (MM): Mechanism of Egression, Clinical Significance and Therapeutic Endpoints
Garces J-J et al
https://doi.org/10.1182/blood-2021-146535

Definition and Clinical Significance of the MGUS-like Phenotype: A Study in 5,114 Patients (Pts) with Monoclonal Gammopathies
Burgos L et al
https://doi.org/10.1182/blood-2021-150092

SARS-CoV-2

There was encouraging data presented by from the iSTOPMM study, showing that after adjusting for age and sex there was no difference in the incidence of severe COVID-19 infection in patients with and without MGUS. This study highlights the differences in COVID-19 disease severity seen in patients with MGUS compared to those reported in patients with smouldering and symptomatic multiple myeloma. Unfortunately, the numbers were insufficient for subgroup analysis, so differences between patients with and without suppressed polyclonal immunoglobulin levels could not be compared. This is an area that needs to be investigated to help us counsel patients more accurately about their personal risk of severe COVID-19 infection.

Promising data on responses following a third dose of mRNA SARS-CoV2 vaccination from the MARS study was presented by Dr Van Oetken. In this study they found that 85% of patients had detectable IgG antibodies against the SARS-CoV-2 spike protein after two doses of SARS-CoV-2 vaccination and that 99% of the responders had an increase in their antibody titres following the third dose of vaccination. Importantly, 81% of the patients who were seronegative after their first two doses of SARS-CoV-2 vaccination developed detectable antibodies following their third dose. Risk factors for non-seroconversion in this study were: receiving daratumumab or anti-BCMA treatment; being in less than a CR; and lymphopenia. These findings are in keeping with the work presented by Dr Fillmore who reported that the highest rate of breakthrough COVID-19 infection was seen in patients being treated with daratumumab.

Monoclonal Gammopathy of Undetermined Significance and COVID-19: Results from the Population-Based Iceland Screens Treats or Prevents Multiple Myeloma Study (iStopMM)
Rögnvaldsson S et al

https://doi.org/10.1182/blood-2021-153145

Suboptimal Humoral and Cellular Immune Response to SARS-CoV-2 RNA Vaccination in Myeloma Patients Is Associated with Anti-CD38 and BCMA-Targeted Treatment
Van Oekelen O et al
https://doi.org/10.1182/blood-2021-152365

Inadequate Sars-Cov-2 Vaccine Effectiveness in Patients with Multiple Myeloma: A Large Nationwide Veterans Affairs Study
Fillmore NR et al
https://doi.org/10.1182/blood-2021-154323

Conclusions

I would like to thank Myeloma UK and Celgene once again for providing me with the opportunity to attend this meeting and giving me the opportunity to share the results of my research project exploring the utility of MALDI-TOF MS testing in patients with multiple myeloma. I would also like to thank the patients who have participated in the Myeloma XI trial and the UK Myeloma Trials Management Group for providing access to the residual serum samples for mass spectrometry testing. I am looking forward to having the opportunity to continue to explore the talks and posters on the virtual platform over the next few weeks and catching up on the data for the emerging novel treatments, such as CAR-T cells therapies and bispecific antibodies.