The MM Hub were delighted to attend Clinical Advances in Myeloma 2018 on 31 January 2018, at the Hallam Conference Centre, London, UK. This was a small conference with approximately 40 attendees and gave us an opportunity to chat informally with local clinicians. The major topics touched upon are summarized in an overview article that can be read here. The first session of the day addressed the topic of Multidisciplinary Perspectives on Myeloma Management and is summarized below.

Changes in Imaging Practices in the UK

The opening session began with a talk by Guy Pratt from the Institute of Immunology and Immunotherapy at the University of Birmingham on the topic of Changes in Imaging Practices in the UK. He began by explaining that bone disease is a major symptom of Multiple Myeloma (MM), and has a big impact on quality of life. He cautioned the use of previous Standard of Care (SOC) regimens, which used skeletal survey (defined by a set of conventional X-rays taken at multiple skeletal sites, such as the skull, spine, chest, femora and humeri), as sensitivity is limited and many changes are not detected until 30–50% of the bone mass has been destroyed. Therefore, the latest guidelines from the National Institute for Health and Care Excellence (NICE) and IMWG criteria now recommend cross-sectional imaging techniques (such as whole-body MRI, low dose whole body CT, and PET-CT), for both diagnosis and assessment of response.

Dr. Pratt referred to the study by Hillengass et al. in which the inferiority of skeletal survey was highlighted – for more information read here. The NICE guidelines as of February 2016 recommend the use of whole-body MRI as the gold standard for first-line imaging, and therefore Dr. Pratt outlined the overall benefits of using whole-body MRI and diffusion-weighted MRI as presented in a study by Rasche et al. - read more here. This study indicated that 11% of patients could be misdiagnosed with the sole use of FDG-PET, and therefore recommends the use of multiple modes of assessment where possible. It was concluded that cross-sectional imaging will become SOC in clinical trials, as it will be used for assessment of drug response, and Dr. Pratt warned that the UK needs to keep up.

The Clinical Relevance of Genetic Markers for Personalized Treatment

The second talk was given by Martin Kaiser from the Institute of Cancer Research and the Royal Marsden Hospital, London. His talk focused on The Clinical Relevance of Genetic Markers for Personalized Treatment. He began his talk by showing the upwards trend of increased survival rates for myeloma patients in the last 40 years but explained that this will only continue to increase with ongoing innovation. He then discussed how the disease is increasingly difficult to treat as it progresses, and noted that we need to limit upfront toxicity in order to achieve longevity. As early disease treatment has the biggest impact, we were advised to “use resources wisely”.

Dr. Kaiser then spoke about the need for personalized therapy. “This is only really in practice in terms of assessing for frailty and patient well-being, but in general, patients are still treated with a one size fits all approach.” He emphasized the need for a truly stratified treatment approach, taking into account individual patient’s genetic status, as well as the fact that the disease evolves genetically over time.
The many genetic mutations that have been linked to MM were outlined, and the inherent mutational heterogeneity of MM is an ongoing consideration. The molecular basis for some of the common aberrations is linked to end signaling effects on NF-κB, Myc, and MAPK signaling pathways. With this in mind, there is a need to move towards the use of molecular diagnostics in MM, and to this end, a comparison of such methodologies with FISH was presented.

**Table 1. Differences between FISH and molecular diagnostics in MM**

<table>
<thead>
<tr>
<th>Quality</th>
<th>FISH</th>
<th>Very targeted (MPLA; qPCR)</th>
<th>Targeted (Panels; Exome)</th>
<th>Comprehensive (WGS; RNA-seq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human factor</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Technical standardization</td>
<td>-/+</td>
<td>+++</td>
<td>-/+</td>
<td>+++</td>
</tr>
<tr>
<td>Throughput</td>
<td>-</td>
<td>+++</td>
<td>+</td>
<td>+({+)</td>
</tr>
<tr>
<td>Infrastructure requirements</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Translocations</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Copy number aberrations</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
</tbody>
</table>

Dr. Kaiser explained that the question we need to address is whether the mutational readouts will really influence the disease outcome, and data from meta-analysis which have come some way to answering this were presented. One such phase III study identified 1,905 Newly Diagnosed (ND) MM patients with several molecular aberrations including high-risk lesions del(17p), gain(1q) and adverse translocations. The loss of heterozygous **TP53** has been shown to correlate with a bad prognosis, although Dr. Kaiser cautioned making such judgments in the absence of gene mutation profiling, as deletions without mutations may not be prognostic. The same is true for chromosome 1q21 copy number gains, with 4 or more copy gains having the biggest impact and indicating a poor prognosis.

Recent studies have displayed new interest in chromosome 1 aberrations, with MCL-1 and SLAMF7 identified as targetable proteins. ‘Double-hit’ myeloma has also been identified as a biomarker to identify poor prognosis in patients with a high degree of certainty. Data from **UK Myeloma Research Alliance (MRA) MUKNine OPTIMUM study** using the GEP SKY 92 profiler was presented, as this gives good discrimination of high-risk versus standard-risk patients, and is clear evidence for a stratified approach.

Dr. Kaiser then talked about the use of Minimal Residual Disease (MRD) assessment to follow treatment response and relapse in high-risk MM. He emphasized that multiple mechanisms of action need to be combined and that triplets are always better than doublets, as they can improve, but not abrogate, the high-risk prognosis. However, it is important to balance efficacy with toxicity. Finally, the use of venetoclax (small molecule BCL-2 inhibitor), as a truly targeted therapy for patients with the t(11:14) translocation, was described, as well as MCL-1 targeting for patients with the molecular aberration ‘gain(1q)’, and vemurafenib to treat BRAF V600 mutated tumors.

Dr. Kaiser concluded with suggestions for ‘Molecular Stratification in 2018’, which should be focused but informative genetic profiling, such as FISH, and if possible extended CNA profiling (eg. MLPA), tests for del(1p) or gain(1q) and if possible gain versus amplification, as well as all IGH translocations, and del(17p). This data must then be corroborated with mutational profiling (eg. for BRAF, KRAS, NRAS, and TP53), and ideally, samples should be stored for future testing. Whole body imaging should be carried out alongside (DWIB or PET-CT).
The molecular landscape for stratified therapy was summarized in a concluding slide. For double hit status, where the proliferation and genetic instability is highest, combination therapies and novel approaches were recommended. For single-hit status, consider intensified and combination therapies, and for other high-risk disease states, such as 1q gain, consider MCL-1 targeting and BCL-2 targeting specifically for t(11;14). For high-risk MM, where possible maintain continuous, multi-agent therapy, as well as clinical trials for both high-risk and NDMM patients.

**Surgical Interventions for Myeloma Bone Disease**

The final talk in this session was given by Susanne Selvadurai from the Royal National Orthopaedic Hospital, who talked about the Management of Spinal Myeloma. Dr. Selvadurai began by highlighting the four main issues for patients with bone damage in myeloma: management of pain, neurological effects, maintaining stability, and avoiding deformity. She then talked through a series of case studies to illustrate how treatment decisions have changed over time, with the use of metalwork and surgical intervention largely now replaced with ongoing bisphosphonate therapy and chemotherapy/thoracolumbosacral orthosis (TLSO) braces. This way unstable spinal fractures can be fixed non-operatively.

Several examples were presented in which cement augmentation was used to help relieve pain and regain stability, although this is not generally used in current practice. Further case studies were presented to address the topic of relieving spinal cord compression. Prophylactic cement augmentation was undertaken occasionally to prevent collapse and the use of kyphoplasty was discussed. In one example, the use of anterior balloon kyphoplasty via the Smith-Robinson approach centered on C5 (no other complications) led to complete pain relief. The Café study of Balloon kyphoplasty versus non-surgical procedures was mentioned, and Dr. Selvadurai cautioned about the possibility of spinal collapse in patients that aren't protected from collapse, even if no neurological symptoms are apparent, as this can lead to long-term deformity. The Spinal Instability Neoplastic Score (SINS) was mentioned, but it was noted that this is not as useful for myeloma as other conditions.

A decision pathway used by the spinal myeloma working group was presented in which patients with abnormal neurology are recommended for a whole body MRI scan, to establish whether there is either soft tissue or bone involvement; with soft tissue only then management will begin with hematology/oncology led treatment, including radiotherapy/chemotherapy. Metalwork should only be considered if there is bone in the spinal canal.

**Conclusion**

These three talks indicate some of the challenges for doctors diagnosing and treating MM. The diagnostic work-up for MM is complex, requiring multidisciplinary input. In particular, the talk from Susanne Selvadurai highlights the importance of considering all aspects of the disease course from the outset. Spinal deformity may be rare, but if the early signs of spinal weakness are not treated, then the outcome can be dramatic. Interdisciplinary communication is also of utmost importance and patients will benefit in treatment centers where this works efficiently.