

American Society of Haematology (ASH)



American Society of Hematology
Helping hematologists conquer blood diseases worldwide



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Introduction

Many of you will already know that the annual 'ASH meeting' is widely regarded as the worldwide premier event in Haematology. There is, therefore, an expectation that any significant progress within the clinical management of MDS will be presented for review. The 57th meeting was held in Orlando, Florida (USA) in December 2015 and was attended by more than 20,000 professionals interested in blood disorders.

Biology of MDS

An increasing number of specific mutations are being identified in patients with MDS. An international collaboration of more than 3000 patients' samples with MDS was presented by Rafael Bejar, Assistant Professor, University of California, San Diego (USA). This provided a wealth of further knowledge on the types of mutations that occur, their potential prognostic impact and potential therapeutic targets.

In future, these investigations will be able to inform which patients might benefit from early therapy, such as stem cell transplantation, those that will not require intervention and those who could be suitable for international collaborative studies of specific rare subtypes of MDS. In the plenary scientific session, there is always justified fanfare as the reviewed abstracts with the greatest merit are given the centre stage in the largest hall. Lee presented work on spliceosomal mutations, demonstrating the importance in the generation of MDS and how they can be modulated by therapy, therefore creating a new therapeutic strategy for future clinical trials.

The recent recognition that the SF3B1 mutation occurs in the majority of patients with ring sideroblasts, as part of their MDS and other similar discoveries, has precipitated an update on the World Health Organisation (WHO) classification of MDS, such that in future "refractory anaemia/cytopenia" will be replaced by "MDS with..." to better describe the subgroups of MDS.

Whilst a lot of these developments in 'genomics' currently inhabit the realms of academic research, rather than conventional NHS therapy, soon the divide will be reduced, in the interim, there are still relatively simple pathology tests (such as P53 staining) that can be very informative in clinical decision-making for clinicians.

Developments in therapy

For me, the main themes explored from a therapeutic perspective were:

1. Treatment options for low risk patients no longer responding to Erythropoiesis-Stimulating Agent (ESA).

Transforming growth factor beta (TGF-B) inhibition

Erythropoietin stimulates the early stages of red cell development. It is recognised in low risk MDS that many patients have abnormal late stage development of red cells. In part, this may be due to excessive growth differentiation factor 11 (GDF 11).

Luspatercept (previously known as ACE-536) is a fusion protein which binds this GDF-11 and other TGF-B proteins, causing a rise in haemoglobin in healthy volunteers. Professor Aristoteles Giagounidis MD, Head of the Department of Oncology, Haematology and Palliative Care, Marien Hospital, Düsseldorf (Germany) presented results of a study in Germany where 58 patients with low risk MDS have been treated, if they've failed or are unlikely to respond to ESA. The majority went on to an extension study where the response rate was nearly 70%, with most responses being long lasting and the treatment well tolerated. An international trial 'MEDALIST' is now being planned.

Other similar agents, such as Sotatercept (ACE-011), are also in clinical development.

2. Telomerase

Most cancers have high levels of telomerase, including the more aggressive forms of MDS. Imetelstat is a strong inhibitor of telomerase which, in clinical trials for myelofibrosis, was found to have a high response rate in patients with specific mutations also common in MDS (SF3B1).

Aref Al-Kali MD (Assistant Professor of Medicine, Mayo Clinic, USA or Tel-Aviv Sourasky Medical Center, Israel) presented the initial findings of a trial in MDS patients with low risk disease, suggesting a good response rate with a reduction in transfusion requirements and good tolerability – again, there are trials planned with the agent in the UK in the near future.

3. Treatment options to improve the response rate with azacitidine

There were a large number of studies looking at combination therapy with the current standard azacitidine. Clearly, the drive here is to improve response rates and therefore survival whilst remaining well tolerated and preserving life quality for patients. Additions to azacitidine included ruxolitinib; pacritinib; lenalidomide; pracinostat; birinapant; vadastuximab and venetoclax. At this stage, most of the combinations seem to have some additive activity but potentially at a cost of additional toxicity and should certainly only be evaluated within clinical trials currently.

Eltrombopag (EPAG) is an oral medication which can stimulate platelet production. Professor Moshe Mittelman MD, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel presented the findings of the ASPIRE study where EPAG was used in patients with advanced forms of MDS and low platelet counts, indicating it appears safe and well tolerated with some activity. Again, it was noted that it can stimulate neutrophil and red cell production. EPAG is currently undergoing trials in the UK in combination with azacitidine (ELASTIC trial).

4. Transplantation

Randomised trials in stem cell transplantation are a rare event partly due to the complexity and the clinician experience with their approach to various clinical transplant situations. The MAVRIC trial was presented by Scott - 272 patients with MDS/AML who were transplanted across 32 transplant centres in the US.

The findings largely supported the already widely held belief that full intensity stem cell transplants are more toxic but have a lower relapse rate when compared to the more frequent approach of reduced intensity conditioning.

Summary

From a clinician's perspective, patients with MDS are all too often a significant challenge with relatively few truly effective therapies available. Our increasing understanding of the biology of the disease is creating more informed treatment decision-making and further therapeutic opportunities which can be explored. Progress in getting new treatments available for patients with MDS has, at times, been frustratingly slow and we are now looking at a future where further licensed therapies in MDS will not be far away.

List of drugs/trials names in this article

Erythropoietin; Sotatercept (ACE-011) – in clinical development; Imetelstat; Azacitidine; Ruxolitinib; Pacritinib; Lenalidomide; Pracinostat; Birinapant; Vadastuximab; Venetoclax; Eltrombopag (EPAG) - EPAG is currently undergoing trials in the UK in combination with Azacitidine.

An international trial 'MEDALIST' is now being planned with Luspatercept (previously known as ACE-536). Trials are planned for Imetelstat with the agent in the UK in the near future. EPAG is currently undergoing trials in the UK in combination with Azacitidine (ELASTIC trial). The MAVRIC trial was presented by Scott - 272 patients with MDS/AML who were transplanted across 32 transplant centres in the US.

MDS UK notes

The ASH website can be consulted freely: <https://ash.confex.com/ash/2015/webprogram/start.html>

Including the ASH patient page: <http://www.hematology.org/Patients/>

MDS Clinical Trials page and Factsheet: <http://www.mdspatientsupport.org.uk/what-is-mds/clinical-trials/>

Do ask about any of these trials at your next appointment. Patients are encouraged to ask about any trials mentioned in our articles and take any articles to their general haematologists. This is important as it will drive haematologists to keep an eye on the latest trials and research news and keep the flow of information moving for patients.