MDS Newsletter

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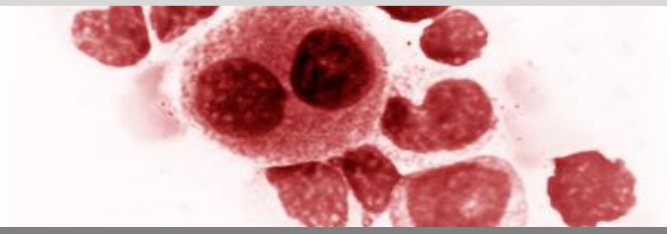
EMSCO
MYELODYSPLASTIC SYNDROMES



Motivation und Mission

The goal of the MDS Newsletter is to promote new knowledge and to support the exchange of information in the clinical research, diagnostics and therapy of myelodysplastic syndromes (MDS).

The newsletter is particularly directed towards clinicians, scientists and industry developers of therapies for MDS. This issue addresses primarily topics like diagnosis and classification of MDS.

Your MDS Newsletter team

7th MDS Colloquium featuring MPN on the 28th and 29th March in Berlin

For the 7th time speakers and guests gathered in Berlin on the 28th and the 29th March to discuss MDS. After the welcome speech by the two chairmen Prof. Dr. med. Uwe Platzbecker (Dresden) and PD Dr. med. Aristoteles Giagounidis (Düsseldorf) 19 contributions in six thematically structured sessions provided insights into morphological particularities, molecular genetic aspects, factors relevant for transplantation, problems regarding iron overload as well as medical therapies for the treatment of MDS. Furthermore presentations on the clinical aspects of MPN were part of this symposium.

Figure 1: Prof. Dr. med. Uwe Platzbecker (Dresden) and PD Dr. med. Aristoteles Giagounidis (Düsseldorf) at the opening speach of the MDS Colloquium 2014

Figure 2: Prof. Dr. med. Ulrich Germing (Düsseldorf) during his presentation on the relevance of morphological examinations for MDS held together with PD Dr. med. Aristoteles Giagounidis (Düsseldorf)

In addition to overview talks three speakers (PD Dr. med. Katharina Götze from München, Prof. Antonio Almeida from Lisbon and Prof. Argiris Symeonidis from Patras) presented selected clinical cases which the audience could interactively assess through the use of a real time voting system. Moreover panel discussions at the end of each session provided the opportunity to ask the speakers questions and to interact with them regarding the presented cases.

Overall 240 participants from 33 countries attended the Colloquium in Berlin of which Germany, the UK, Switzerland, Russia and Spain represented the nations with the proportionally biggest share of attendees.

Figure 3: Group foto of the 7th MDS Colloquium featuring MPN

A warm thank you for the successful outcome of the event goes to all organizers, speakers, and participants as well as the main sponsor Celgene.

Author: Silke Gloaguen

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GMIHO
Gesellschaft für Medizinische Innovation – Hämatologie und Onkologie mbH
Managing Director:
Claus-Peter Held

Address:
GMIHO mbH
Alte Jakobstraße 77,
10179 Berlin
Phone:
+49 351.25933-280
Fax:
+49 351.25933-289
Email: info@gmiho.de
https://www.gmiho.de

registered at Berlin-Charlottenburg District Court (Amtsgericht)
HRB 101719 B

VAT-ID
DE 250223501

Editors:
Silke Gloaguen
Denise Lippmann

Layout:
Denise Lippmann

Photo credits:
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MDS classification: WHO meeting in Chicago in April

Based on the ground-breaking work of 1982 (1) of the French-American-British work group (FAB) which had for the first time elaborated a uniform classification of pre-leukaemia our knowledge regarding the diagnosis, prognosis and therapy of myelodysplastic syndromes (MDS) has significantly broadened. Triggered by the work of the Düsseldorf work group on the heterogeneity of sideroblastic anaemia in 1990 (2) a new classification for MDS was proposed in 1997, taking into account the extent of dysplastic signs of the different cell lines, the extent of clonal expansion and for the first time chromosomal findings (3). The classification was evaluated in a prospective manner (4) and acted as the foundation of MDS classification which had been refined for the last time in 2008 (5). However, this classification became increasingly complex and difficult to use, which is why some of its clinical aspects began to be questioned in daily clinical routine and in the context of scientific investigations (6). Nevertheless, when used correctly, this classification delivers a plethora of prognostic information which provides, together with prognostic scores (7,8), a good diagnostic basis for clinical trials and it has gained acceptance in most countries.

In April 2014 a group of pathologists and haematologists met again at the University of Chicago to intensively discuss changes within the classification. It was not primarily about developing a completely new classification rather about improving individual aspects and definitions and to make it more user-friendly. The discussion mainly focused on the MDS types RCUD, non-classifiable MDS and MDS with del(5q), on the integration of molecular findings and on questions of nomenclature. Unfortunately our pathophysiological knowledge of MDS is still too fragmentary to be able to elaborate a classification being primarily based on pathophysiological understanding. The proposals that have been developed in the group will now be discussed by the work groups of the pathologists and in the course of 2015 a new classification of MDS will be published by the WHO in collaboration with pathologists and haematologists.

The extremely exciting meeting in Chicago has shown that we can go forward based on new insights, step by step, and that this is to an extent is due to contributions from the German MDS group.

Author: Prof. Dr. med. Ulrich Germing

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Role of molecular markers for diagnosis and treatment decisions in myelodysplastic syndromes

The diagnostic evaluation of myelodysplastic syndromes (MDS) has not changed significantly in the last 30 years and still relies on peripheral blood findings, bone marrow examination, which can show poor interobserver reliability, and metaphase cytogenetics of a bone marrow sample. However, diagnosis of MDS remains difficult in some cases.

The molecular basis of MDS is only beginning to be elucidated. Gene expression profiling (GEP) and genetic abnormalities detectable by single nucleotide polymorphism arrays (SNP-A), but not by metaphase cytogenetics, have both been associated with the prognosis of MDS. However, neither the GEP nor SNP-A testing is standardized and the manner in which they are analyzed could affect their prognostic significance. Currently, neither test is really considered part of the standard of care for any myeloid malignancy (1).

Conversely, somatic mutations are less challenging to detect and are routinely evaluated in the management of patients with other myeloid malignancies. With the development of whole-exome and whole-genome sequencing, the number of genes affected by somatic mutations in MDS has grown dramatically over the last few years, making these abnormalities much more prevalent than cytogenetic abnormalities (1). Given the remarkable advances in next-generation sequencing (NGS) technologies and ever dropping costs, multiple platforms are now becoming available for mutational profiling in clinical practice. Therefore, testing for the presence of these mutations in peripheral blood or bone marrow using NGS assays is likely going to become routine.

Recurrent somatic mutations of more than 40 genes have been identified in MDS. The genes mutated in MDS can be classified into several categories: (I) transcription factors (e.g., TP53, RUNX1, ETV6, PHF6), (II) epigenetic regulators and chromatin-remodeling factors (e.g., TET2, DNMT3A, ASXL1, ATRX, IDH1/2, EZH2), (III) pre-mRNA splicing factors (e.g., SF3B1, U2AF1, SRSF2, ZRSR2), and (IV) signaling molecules (e.g., NRAS, PTPN11, CBL, JAK2, NPM1). Approximately 80-90% of the patients, if not all, harbor at least one such disease-driving mutation. However, the vast majority of mutations are rare (< 5%) and no specific mutation is present in more than one third of MDS patients. The splicing factor SF3B1 is the most frequently mutated (15-30%), followed by TET2 (15-25%), ASXL1 (10-20%), SRSF2 (10-15%) and RUNX1 (10-15%). Collectively, about 45% of MDS patients have mutations in U2AF1, ZRSR2, SRSF2, or SF3B1 (1-5).

Although the identification of somatic mutations can help in the diagnosis of uncertain cases of MDS by providing a marker of clonality, the presence of an MDS-associated somatic mutation can at least confirm the presence of clonal hematopoiesis but not the MDS diagnosis. Indeed, it has been found that elderly individuals without any evidence of hematological malignancy can acquire clonal hematopoiesis as a consequence of aging, for example with somatic TET2 mutations (6).

Because of wide variation in the clinical course of MDS, the prediction of prognosis is of particular importance for MDS patients. Multiple classification and prognostic scoring systems have been developed to identify MDS subtypes or risk groups with similar outcomes. These schemes are based on morphology, clinical variables such as cytopenias, and cytogenetics. Somatic mutations are fundamental determinants of MDS pathophysiology, but are not yet part of any of the existing risk stratification systems (2).

In 2011, Bejar et al. showed that somatic mutations in several genes could add prognostic information independent of models such as the International Prognostic Scoring System (IPSS). In particular, mutations of TP53, EZH2, ETV6, RUNX1, and ASXL1 were each found to identify patients with shorter survival than predicted by the IPSS (3). More recently, Haferlach et al. investigated the presence of mutations/deletions in 104 genes using targeted deep sequencing and array-based genomic hydridization in a large cohort of MDS patients. Alterations in 25 genes significantly affected survival in univariate analysis and the status of 14 genes was found to predict survival in

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>>> multivariate analysis. Further combining the 14 prognostic genes with conventional risk factors such as age, gender, and the parameters used in the recent revision of IPSS (IPSS-R) allows discrimination of 4 significant risk groups, and better predicted survival than “gene-only model” or IPSS-R (5).

One of the major advantages of NGS compared to Sanger sequencing relies in the possibility to assess the mutant allele frequencies for different somatic mutations, and thereby the size of each clone or subclone. Recently, Papaemmanuil et al. reported that driver mutations had equivalent prognostic significance, whether clonal or subclonal, and that leukemia-free survival deteriorated steadily as numbers of driver mutations increased. Another important finding of this study is that one of the strongest outcome predictors is the total number of driver mutations identified in a patient, so that sequencing a comprehensive set of well-characterized genes is critical for use in diagnostic screening (4).

Other than del(5q) for lenalidomide and serum erythropoietin levels predicting response to erythropoiesis-stimulating agents, there are no widely used biomarkers to guide treatment decision in MDS patients. Somatic mutations may serve as such biomarkers if they can be shown to consistently predict treatment response. In a retrospective cohort of MDS patients treated with azacitidine, the presence of a TET2 mutation was found to be associated with an 82% response rate, compared with a 45% response rate in TET2 wild-type patients (7). In a recent phase 2 study of lenalidomide and azacitadine in patients with IPSS-intermediate and high-risk MDS, the presence of TET2, DNMT3A, IDH1, or IDH2 mutations was predictive of achieving complete response (8). Additional studies designed to identify genetic predictors of response to different treatment modalities, such as hypomethylating agents or allogeneic stem cell transplantation, are needed for tailoring appropriate therapy to each patient.

In conclusion, integration of somatic mutation assays into MDS diagnosis, risk stratification, and prediction of therapeutic response has the potential to greatly improve treatment outcomes for MDS patients. In addition, better understanding of the biologic basis of MDS will be helpful for the design of targeted therapies.

Author: Dr. Aline Renneville

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MDS experts presented:
Prof. Dr. med. Ulrich Germing - University Hospital Düsseldorf

Prof. Germing is a leading senior physician (Oberarzt) and deputy director at the Department of Haematology, Oncology and Clinical Immunology at the University Hospital in Düsseldorf.

He was born in Dortmund in 1965 and started his medical training in the summer semester of 1986 at the University of Düsseldorf. After his approbation in 1992 he worked as a resident at the Department of Haematology, Oncology and Clinical Immunology (director: Prof. Dr. med. Rainer Haas), in cardiology and in gastroenterology and he obtained his doctoral degree in 1994. In 1997 Prof. Germing obtained the certification as a specialist for Internal Medicine and he is a senior physician in the aforementioned department since 1999.

In 2001 Prof. Germing has habilitated in the field of Internal Medicine and in the same year he obtained the certification as a specialist for Haematology and Internistic Oncology.

Since 2000 Prof. Germing works as a subproject leader in the Competence Net Acute and Chronic Leukaemia “prognostic evaluation for patients with MDS”, in 2002 he founded the German-Austrian-Swiss MDS work group and since 2004 he is involved in the European LeukemiaNet. In 2007 he was appointed a member of the Clinical Advisory Conference of the WHO for the classification of haematological diseases.

Prof. Germing is author of more than 200 publications listed in Pubmed, he is married and has two sons.

Overview of event recommendations

3rd French-German MDS Workshop
2nd Annual EMSCO-Meeting

10th to 11th September 2014
NH Dresden Altmarkt – Germany

http://www.emsco.eu/workshop

EHA 2014 - 19th European Hematology Association Congress
12th to 15th June 2014 | Medical Congress Milano - Italy
More information: http://www.ehaweb.org

Jahrestreffen der Deutsch-Österreichisch-Schweizerischen MDS-Studiengruppe
24th September 2014 | University Hospital Düsseldorf - Germany

MDS Forum 2014
7th to 8th November 2014 | Frankfurt/Main - Germany

56th ASH Annual Meeting and Exposition
6th to 9th December 2014, San Francisco - USA
Mehr Informationen: http://www.hematology.org/Annual-Meeting

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