MDS Newsletter

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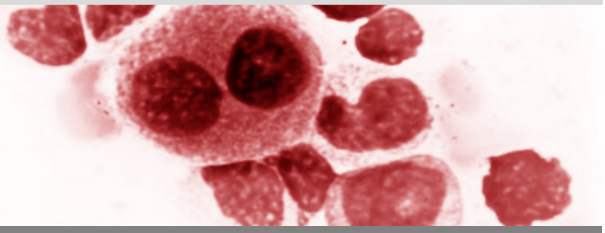

Motivation und Mission

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.

Kind regards,
Silke Gloaguen in the name of the EMSCO team

Activities of the German-Austrian-Swiss (D-A-CH) MDS Group

Since the 1980s, first scientific MDS activities have started to grow in Germany and Austria. On one hand, considerations about diagnosis and prognosis of MDS patients have led to the establishment of the MDS Registry in Düsseldorf in 1982 under the direction of Prof. Aul.

On the other hand numerous clinical trials, which predominantly took place in Hannover, Düsseldorf and Freiburg, were initiated. Cytokines, erythropoietin, GMCSF, interleukins, all-trans retinoic acid but also chemotherapy protocols available at that time including low dose AraC were investigated in mostly monocentric trials and consequently published.

Then, another subject of relevance for MDS was essentially promoted by colleagues from Göttingen, namely the importance of cytogenetic findings for MDS patients. Important stimuli on this topic also came from Austria were traditionally several important MDS sites are located. Initially the sites of Innsbruck and Linz were very active, later on the sites from Vienna (Hanusch Hospital and the university) joined in.

Over time, the teams from the different sites gradually became acquainted with each other as they met at conferences – especially at the ones of the "International MDS Foundation". By the end of the 1990s it became more and more obvious that a close cooperation between different sites would allow for a more efficient handling of scientific questions - primarily regarding prognosis and pathophysiology but also in terms of clinical trials. Partly triggered by the activities of the competence network "acute and chronic leukemias", a formal network structure was established and support was provided for the participating sites.

In 2001, predominantly incited by Düsseldorf and Göttingen, a working group was launched with the objective to collectively tackle prognostic questions. Starting point was the awareness of certain shortcomings of the IPSS score, which were to be evaluated with the help of a common data set. The first meeting of our working group took place in Düsseldorf in September 2001. Besides Düsseldorf and Göttingen the Johannes Hospital in Duisburg, the Medical University of Vienna, the Hanusch Hospital in Vienna, the Hospital "Barmherzige Brüder" in Linz and the University Hospital of Freiburg were founding members of the working group.

The core agreement of the working group, which is still valid today, was to exchange data and biomaterial for the purpose of scientific projects in the field of MDS and to initiate projects submitted by members and consequently led by the site having suggested the initiative. However, the individual sites decide independently on the contribution of data and biomaterial. This approach ensures that the data and the material remain in possession of the sites and that the various projects are led and coordinated by different sites. Therefore the definition of a consistent minimal data set was required to allow for an efficient data exchange and to achieve the best possible >>>

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level of documentation. This common data set facilitated many projects in order to investigate and enhance MDS prognosis. In particular, it allowed for substantial improvements in the field of cytogenetically driven prognosis based on research orchestrated by Göttingen. These efforts finally led to the development of the IPSS-R. The German-speaking MDS community has thereby impressively demonstrated that essential and new scientific enrichment is to be expected from this part of the world.

In the course of time the cooperation was broadened and important sites such as Munich, Dresden, Mannheim, Hannover, Lausanne and many others joined with new ideas, data and material so that, over the years, a quite big and well-balanced group of different collaborators from many sites emerged. With time the activities of the group resulted in numerous publications, either by the working group itself or as joint efforts in collaboration with international partners. All publications can be found on our website www.mds-register.de.

In parallel to this development, the German sites closely cooperate by implementing common clinical trials, in particular IITs. Thus, the sites also play an important role in this field seen from an international perspective.

Following the approval of three new MDS medications in Europe, the pharmaceutical industry started to show interest in MDS. This interest for instance translates into financial support for the MDS registry, which is coordinated by GMIHO. Participating sites can therefore get support for their projects and since last year this support has been formalized by new contracts between the sites and GMIHO.

Last but not least our group has originated a collaborative MDS project funded by the German Cancer Aid. This collaborative project is led by Mannheim and it supports some of the sites to conduct scientific projects for a period of 3 years. In the context of this project the biobank in Düsseldorf was formally opened for interested sites and by now, clinical data and material from over 600 MDS patients have been included. Proposals for the use of the material and the data for scientific purposes can be submitted.
Each year our group meets in Düsseldorf to discuss new initiatives and the progress of ongoing projects. This year our 15th annual meeting takes place on September 23rd in Düsseldorf and everybody who is interested is cordially invited to attend.

In the name of the D-A-CH Working Group
Ulrich Germing

MDS is in the niche

Myelodysplastic syndromes (MDS) represent clonal disorders mainly of the elderly that are characterized by ineffective hematopoiesis and an increased risk of transformation into acute myeloid leukemia. The pathogenesis of MDS is thought to evolve from accumulation and selection of specific genetic or epigenetic events. There are several well described somatic genetic abnormalities, which are commonly, although not exclusively, found in MDS. At least one genomic alteration can be found in 78% of MDS patients, with genes involved in RNA splicing (SF3B1, SRSF2) to be the most common and the earliest in disease evolution *(Papaemmanuil E et al., 2013)*. Although the most important event in MDS pathology appears to be a molecular defect in hematopoietic stem and progenitor cells (HSPC), evidence suggests that ineffective hematopoiesis may also result from abnormalities in the bone marrow microenvironment, including altered hematopoietic-stromal interactions and deregulated production of growth factors and hematopoietic modulators. The alterations of niche cells have been demonstrated in the majority of studies. The first report revealed decreased osteoblast and osteoclast numbers and bone formation rate *(Mellibovsky L et al., 1996)*. Recently, an association of high CD271+ MSPC density with shorter overall survival among patients with MDS has been observed (Johnson RC et al., 2014). Multiple data have demonstrated reduced osteogenic differentiation and low ability to support hematopoiesis in LTC-IC assays *(Gayh S et al., 2013; Zhao ZG et al., 2012)*. CD49b – an integrin >>>

involved in the interaction of mesenchymal stem and progenitor cells (MSPCs) and collagen type I – is expressed at a higher level that can implicate changes in extracellular matrix synthesis and MSPC growth defects *(Flores-Figueroa E et al., 2008; Aanei CM et al., 2012)*. MSPCs display a more widespread expression of CXCL12 in MDS, which may expose HSPC to increased contact-mediated signaling with CXCL12-expressing cells. Thus, these stromal cells fail to support trafficking of maturing hematopoietic cells to the microenvironment compartments *(Flores-Figeuroa E et al. 2012)*. On the other hand CXCR4 expression on HSPC has been found to be downregulated in MDS that could be successfully corrected by treatment with lenalidomide *(Ximeri M et al., 2010)*. Various cytogenetic abnormalities have been shown to be present in MSPCs of up to 50% of patients with MDS, which are different from those, detectable in the HSPC compartment *(Pimenova MA et al., 2013)*. The issue of secreted cytokines and adhesion molecules in MDS is controversial, as some groups claim no difference in cytokine status between MDS patients and healthy donors, whereas the others demonstrate profound deregulation of secretion of VEGF, LIF etc. and highly upregulated N-cadherin expression in MDS-MSPCs (Medyouf H. et al., 2014). An increased production of Il-1β and SCF was observed in response to TNFα stimulation *(Matsuoka A et al., 2010)*, whereas TNFα secretion itself induced conflicting data with a proposal of its possible role together with IFNγ in disease progression *(Ishibashi M et al., 2011)*.

The impact of deregulated Wnt signaling in MSPCs on MDS pathogenesis remains largely elusive. Genes encoding known Wnt antagonists have been shown to be hypermethylated in patients with MDS *(Reins J et al., 2010)*, suggesting a direct correlation between methylation status and risk of leukemia evolution *(Wand H et al., 2013)*. On the other hand, global gene expression profiling showed a significant down-regulation of genes involved in canonical Wnt signaling, especially in the 5q- syndrome. This data led to the hypothesis that the imbalance between canonical and non-canonical Wnt signaling may contribute to the defective self-renewal of HSPC *(Pavlaki KI et al., 2011)*. This altered signaling is also suspected to play a role in iron regulation and appears to be an important player in MDS pathogenesis, which requires further studies. Of note, deregulation of Wnt signaling not only affects HSPC, but also has an influence on the bone marrow niche (Luis TC et al., 2012). As such, overexpression of various Wnt-inhibitors in OB exhibits a dual effect by altering the niche architecture with the reduction in trabecular bone and affecting hematopoietic progenitor cells *(Schaniel C et al., 2011; Fleming HE et al. 2008; Renstrom J et al., 2009)*, both impairing their localization and function within the bone marrow (Lane SW et al., 2011). Depletion of iron can activate Wnt/β-catenin pathway and induce osteoblastic differentiation of MSPCs *(Qu ZH et al., 2008)*. However, it remains to be seen whether this has implications in the clinical setting, when iron chelation is administered to MDS patients. Importantly, activating mutation of β-catenin in OB, also found in patients with MDS, led to the increased synthesis of Notch ligand Jagged 1, which in turn activates Notch signaling in HSPC, leading to alteration of differentiation potential of hematopoietic progenitors and AML development *(Kode A et al., 2014)*. This coupling of stromal and hematopoietic signaling pathways clearly highlights the need for developing new strategies aiming at disrupting this pathological niche-hematopoietic cell interaction.

Complex interactions between hematopoietic cells and their niche provide a rationale for developing a holistic osteo-hematological approach in the treatment of MDS. One of the best examples of such approach can be demonstrated by means of allogeneic hematopoietic stem cell transplantation (HSPCT). Engraftment and maturation of donor-derived multipotent HSPC defines the success of this approach. The prerequisite for that is an appropriate milieu provided by a competent bone marrow microenvironment which is chimeric following allogeneic HSPCT, containing recipient MSPC-derived cells and donor monocytes/macrophages. Thus, when allogeneic stem cells are infused, they encounter a microenvironment which is possibly impaired for a sustained period of time. This may in part explain the higher rates of graft failure and relapse as well as the prolonged time to stable engraftment seen in MDS patients mainly after HSPCT with reduced intensity conditioning. Given the long-term engraftment in this group of patients, irreversible

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MSPC defects seem rather unlikely and the problems are probably more related to disturbed cross-talks between hematopoietic cells and the bone microenvironment. On the other hand, allogeneic HSPCT might reprogram the microenvironment by modulating other HSPC-derived compartments including osteoclasts. Comparative analyses on the functional capacity of the microenvironment in MDS prior to and after allogeneic HSPCT are not yet available.

Two hypomethylating agents (HMA) – azacitidine and decitabine – which were originally thought to affect only the defective leukemic clone are now shown to have an influence also on the bone cells. As such, azacitidine inhibits the Wnt-signaling pathway in MDS cells and might improve bone metabolism as well *(Masala E et al., 2012)*. Further, HMA could increase expression of BMP molecules in osteoblasts, thus potentially favoring the process of bone formation compared to bone resorption *(Delgado-Calle J et al., 2013)*.
The most prominent example of potential simultaneous effect represents the activin receptor type II ligand trap sotatercept (ACE-011) *(Dussiot M et al, 2014)*. Its main action is antagonizing activin and other ligands of the TGFβ-family and interfering with downstream signaling cascades, mainly the SMAD pathway. Activin levels correlate with bone lesions and in the preclinical studies ACE-011 increased bone formation, mineral density and strength of trabecular bone in monkeys *(Lotinun S et al., 2010)*. Concurrent prevention of paclitaxel-induced anemia in murine models *(Mulivor AW et al., 2009)*, as well as observed increase in hemoglobin in patients, treated with this drug for postmenopausal osteoporosis *(Ruckle J et al., 2009)* and myeloma bone lesions *(Abdulkadyrov KM et al., 2014)*, led to the idea that ACE-011 could have an impact on erythropoiesis either directly or by modifying the functions of bone cells. However, it does not affect differentiation of erythroid progenitors or precursors directly, thus this effect is expected to be mediated by factors present within bone marrow niche *(Carrancio S et al., 2014)*. Indeed, stromal cells showed alterations in the expression of various important genes and cytokines in response to the drug *(Iancu-Rubin C et al., 2013)*. These findings indicate that sotatercept/ACE-011 and ACE-536 may represent effective treatments for impaired erythropoiesis in MDS with concomitant alterations of the osteo-hematopoietic niche. Currently two clinical trials are recruiting patients to evaluate the effect of activin receptor type II ligand trap on anemia in patients diagnosed with MDS (ACE-011/sotatercept - NCT01736683; ACE-536/luspatercept - NCT02268383) and preliminary data suggest clinical activity *(Platzbecker U et al., 2014)*.

Another approach to interfere with the osteo-hematopoietic niche in MDS might be through counteracting the phenomenon of iron overload. The mainstay of systemic iron overload treatment is nowadays iron chelation. Various mechanisms have been proposed to mediate its effect on hematopoiesis, such as reduced oxidative stress and improved stromal support *(Lu WY et al., 2013)*. Indeed, deferoxamine could partially attenuate MSPCs injury and inhibit signaling pathways induced by excessive iron. A role for iron chelation in the improvement of stromal cells function and their ability to support hematopoiesis is yet to be reported. Other treatment options, which influence the hepcidin-ferroportin axis, including hepcidin analogs and signaling antagonists, transferrin or BMP6, could provide an effective alternative and are currently under investigation. In general, the regulation of hepcidin-ferroportin system could be an important approach in iron overload accompanying MDS, but the side effects, such as iron deficiency or excessive calcification should be avoided.

Taken together, MDS represents a disease with vivid interactions within the osteo-hematopoietic niche and the contribution of the niche has only recently been appreciated. Thus, treatment strategies need to be developed that not only target the leukemic cells, but also the signaling pathways connecting both sides to provide a holistic and effective approach to this disease.

Author: Ekaterina Bulycheva

This text represents a short version of the article by Bulycheva E. et al. "Myelodysplasia is in the niche: novel concepts and emerging therapies", Leukemia, 2015 Feb;29(2):259-68.

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Progress of the EUROPE trial

Prospective validation of a predictive model of response to romiplostim in patients with IPSS low or intermediate-1 risk myelodysplastic syndrome (MDS) and thrombocytopenia

Having already started the DACOTA trial in October 2014, we are now happy to announce the launch of the second trial in collaboration between several European MDS study groups under the common umbrella of "EMSCO". Indeed, this trial will be carried out by the German and French study groups and as the French group GFM acts as sponsor for the DACOTA trial, Germany now assumes this role for EUROPE. Prof. Uwe Platzbecker from Dresden is lead PI in this common project.

Background and rationale for the trial

Romiplostim is an Fc-based fusion protein binding to and stimulating the thrombopoietin (TPO) receptor. Based on two clinical trials (Giagounidis et al., 2014; Kantarjian et al., 2010) evaluating romiplostim in LOW/INT-1-MDS patients with predominant thrombocytopenia, an international expert group developed a predictive model in order to identify patients potentially benefitting from treatment with romiplostim in a targeted way (Sekeres et al., 2014). This work considered the HI-P (hematologic improvement of platelets) as well as the ≥50% response (defined as an increase in thrombocytes over a period of 50% or more of the total treatment period) in relation to (a) baseline serum TPO levels and (b) the number of previously received platelet transfusions. The resulting model differentiates three romiplostim response groups based on the calculated scores (see figure 1), whereas highest response rates can be observed in patients with low (<500 pg/ml) TPO levels and comparatively few (<6 units) previous platelet transfusions. This predictive model is hence similar to the EPO-level-based model for the treatment of anemia with erythropoietin.

This model, which has been developed based on retrospective data, is now to be prospectively validated by the EUROPE trial.

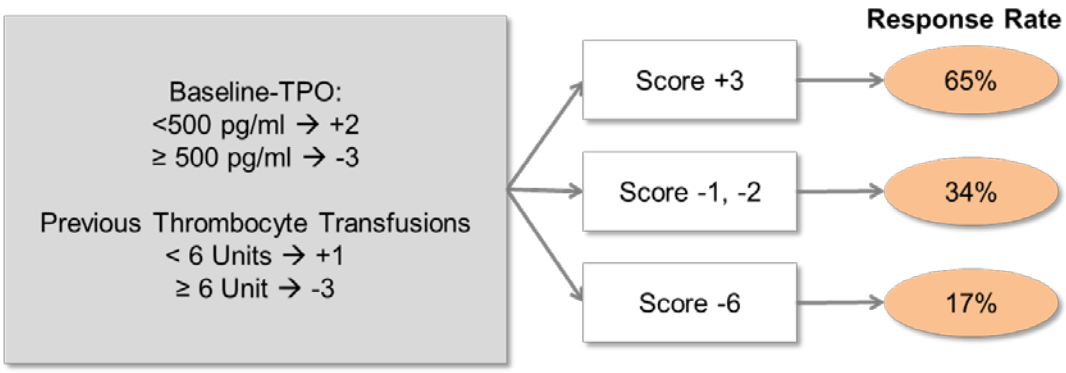

Figure 1: TPO-based model to predict subsequent response to romiplostim in MDS patients with IPSS LOW/INT-1 according to the model developed by Sekeres et al., 2014

Trial characteristics

The EUROPE trial has been designed as an open-label, single-arm multicenter, phase II study with the aim to enroll and stratify 90 patients in Germany and France according to their scores calculated based on the model described above. The main trial characteristics are summarized in table 1.

As mentioned above, the patients enrolled in the trial are assigned to three different cohorts after screening. After the final statistical analysis, the model prediction will be considered successful if the best model group (score +3) achieves a significant better HI-P response rate after four months than the intermediate group (score -1, -2) and the worst group (score -6). Figure 2 depicts the overall treatment scheme, including the assignment to the three cohorts.

SHORT TITLE:	EUROPE
EudraCT NUMBER:	2013-004328-12
STUDY DRUGS:	Romiplostim (Nplate®)
INDICATION:	IPSS low and int-1 MDS patients with thrombocytopenia
FINANCIER:	Amgen

TRIAL OBJECTIVES:

- Primary: to investigate prospectively whether the current TPO level based response model can predict response to romiplostim in thrombocytopenic patients with IPPS LOW/INT-1 MDS
- Secondary: Safety, bleeding events, AML evolution, peripheral blasts during therapy, identification of molecular parameters associated with response and progression

TRIAL DESIGN:

This is an open-label, single-arm multicenter, phase II study

ENDPOINTS:

Primary:

- Hematologic improvement of platelets (HI-P) after 4 months on therapy

Secondary:

- Cumulative hematologic improvement of platelets (HI-P), erythrocytes (HI-E) and neutrophils (HI-N)
- The incidence of disease progression to higher stage MDS or AML
- Increase of peripheral blasts during therapy
- Association of the presence of certain mutations with disease progression in a retrospective analysis
- Incidence of bleeding events
- Type, incidence and severity of all adverse events including clinically significant changes in laboratory values

TIMELINES:

Recruitment:	36 months
Min. treatment duration (non-responders):	4 months
Max. treatment duration responders):	12 months
Follow-up for all patients:	12 months
Overall trial duration:	60 months

TOTAL SAMPLE SIZE:

At least 100 patients screened for a total enrollment of 90 patients

Table 1: Summary of the EUROPE trial characteristics

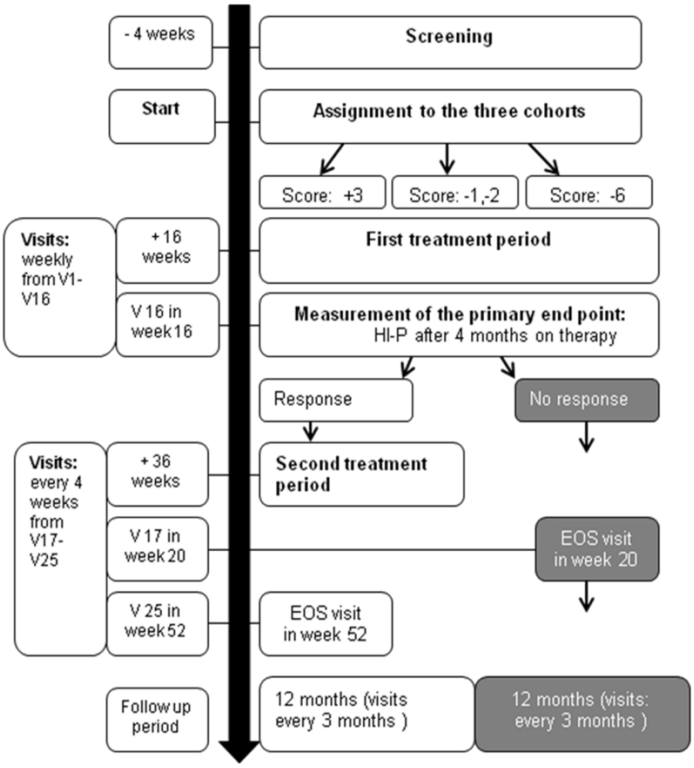

Figure 2: Treatment scheme within the EUROPE trial (grey boxes represent patients to whom no study drug is administered)

Progress of the trial

Approval by the principal ethics committee (Dresden, Germany) has been obtained on January 23rd 2015 and the German competent authority (PEI) has authorized the current protocol version on April 16th 2015. Now, the first sites have been opened and the first patients are screened in Germany. Furthermore, all relevant and finalized documents have been transferred from the German study coordinators to the French team in order to launch the approval process and get the French sites started as well.

We are very happy to have established this second collaboration and we are looking forward to a successful recruitment and positive outcomes.

Authors: Silke Gloaguen and Annegret Böttner

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Overview of event recommendations

4th French-German MDS Workshop
17-18 September 2015 – Marseille, France
More information: http://www.emsco.eu/workshop/

15th Annual Meeting of the German-Austrian-Swiss (D-A-CH) MDS Working Group
23 September 2015 - Düsseldorf, Germany

8th MDS Colloquium
06-07 November 2015 – Berlin, Germany
More information: http://www.mds-colloquium.de/