MDS Newsletter

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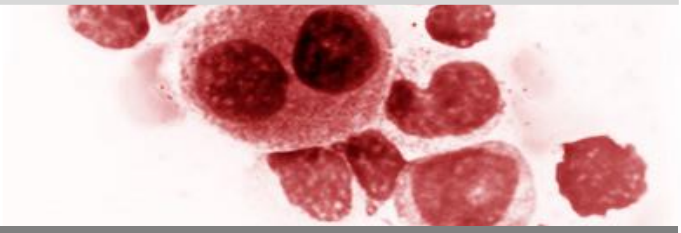
EMSCO
MYELODYSPLASTIC SYNDROMES



Motivation and 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).

This newsletter is particularly directed towards clinicians, scientists and industry developers of therapies for MDS.

We provide information on various topics such as current clinical trials, new methods of diagnosis and treatment options, research reports as well as current events regarding MDS.

If you would like to submit information to be included in the next newsletter please contact us at **info@gmiho.de**.

Your MDS Newsletter team

Review - EMSCO Kick-Off within the framework of the 2nd French-German MDS Workshop in Paris

On 18th and 19th September 2013 the second annual meeting was held by the French and German MDS Study Group. Experts from both countries jointly discussed the current diagnostic and therapeutic strategies for MDS.

Within the framework of this event, the Kick-Off meeting for EMSCO was held.

EMSCO is a Study Coordination Office, which was founded in early 2013 for the coordination of clinical trials in the field of MDS. The networking of researchers, study groups and industry creates an open cooperative environment which ultimately benefits both MDS research and patients. The services of EMSCO include the development of clinical trials, protocol review and CRF design, as well as support for principle investigators in costing, providing necessary documents and forms, drafting of contracts and in the coordination of clinical MDS studies and projects.

At the Kick-Off event on 18th September 2013, experts met to jointly discuss future strategies to increase the quality of clinical studies in the field of MDS. In addition, possible starting points for the standardization of trial documents, CRFs and working instructions (SOPs) for MDS trials were discussed. This meeting was organized by the GMIHO mbH.

A special thanks go to the sponsors Celgene GmbH, Boehringer Ingelheim, Novartis and Baxter Oncology GmbH for their support for the implementation of the events.

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Current MDS trials in Germany

Clinical trials are essential to improve treatment options for MDS patients. There are numerous innovative clinical trials currently enrolling MDS patients in Germany as well as trials in the planning phase set to begin enrollment within the next 12 months. This summary focuses on trials currently open for enrollment in Germany.

Lower-Risk MDS according to IPSS

In anemic patients with lower risk MDS according to IPSS, two large phase III randomized placebo controlled trials are evaluating the efficacy of erythropoietin (EPO) to raise hemoglobin levels (EPOANE trial, Darbepoetin trial). These trials are expected to lead to licensing of erythropoietin for MDS in the future.

For patients who cannot be included into one of these trials due to high intrinsic EPO levels or who have failed EPO treatment, current options include participation in the A536 (PACE) trial or the APG101 trial. The former is a phase II open-label dose-escalation study assessing the rate of erythroid response in anemic patients (either non-transfusion or transfusion dependent). ACE 536 is a recombinant fusion protein consisting of a modified form of the human activin receptor type IIB linked to the human IgG1Fc domain, acting as a ligand trap for TGFbeta and other ligands.
The APG101 trial is a phase II open label study evaluating safety and tolerability of APG101, a soluble CD95-Fc fusion protein blocking the interaction between CD95 and FAS ligand, in transfusion dependent MDS patients.

For lower-risk MDS patients suffering from thrombocytopenia in addition to transfusion dependent anemia, the AZA-MDS-003 trial evaluating the efficacy of oral azacitidine is an attractive therapeutic option. This is a randomized placebo controlled double-blind phase III trial.

Study	EPOANE-Study	Darbepoetin-Study	A536 (PACE)-Study	APG101-Study	AZA-MDS-003-Study
Target	Assess the efficacy of EPO to increase hemoglobin values		Assessment of the extent of erythroid response in anemic patients	Assess the safety and tolerability of APG101 (soluble CD95-Fc fusion protein)	Assessment of the efficacy of oral azacitidine
Target group	Patients with low extrinsic EPO values		Patients with high intrinsic EPO values		Patients with transfusion-dependent anemia and thrombocytopenia
Phase	Phase III	Phase III	Phase II	Phase II	Phase III

Figure 1: Overview studies Lower-Risk MDS according to IPSS

Higher risk MDS according to IPSS

Trial options for patients with higher risk MDS include the temsirolimus trial, which evaluated the efficacy of temsirolimus in patients intolerant or refractory to azacitidine. This trial has recently been closed. Previously untreated patients with higher risk MDS can participate in an open-label phase I dose escalation trial testing the combination of azacitidine with the polokinase inhibitor volasertib. After completion of the dose escalation part of the trial, an expansion phase including a larger number of patients will commence. For patients generally eligible for allogeneic stem cell transplantation, a trial testing the value of azacitidine as a bridging therapy prior to transplantation is an attractive option. In this study, all patients receive 4 cycles of azacitidine. Patients lacking a suitable stem cell donor will continue azacitidine treatment while patients with a suitable donor will then proceed to allogeneic transplantation. MDS patients who have already successfully undergone allogeneic transplantation can enroll in the RELAZA trial. This innovative trial closely monitors transplanted patients by MRD for signs of imminent relapse. Patients who become MRD positive but are still in hematologic remission will be treated with azacitidine in an attempt to prevent full-blown relapse.

In December 2013 a phase I clinical trial of romidepsin as an add on to 5-azacitidine in higher-risk MDS after insufficient response to 5-azacitidine monotherapy or relapse after treatment with 5-azacitinide has been initiated at the UKD-Düsseldorf (ROMDS). Patients with MDS of IPSS INT-2 or high risk who are not eligible for hematopoietic stem cell transplantation and do not respond to 5-azacitidine have a very poor prognosis and there are currently no other therapeutic options. The primary objective of the trial therefore is to determine the maximum tolerated dose (MTD) for the treatment with the HDAC inhibitor romidepsin in combination with 5-azacitidine, as well as the tolerability and response rate of this treatment regimen. Likewise MDS patients, as well as patients with chronic myelomonocytic leukemia (CMML) or patients with acute myeloid leukemia (AML) who are not eligible for haematopoietic stem cell transplantation and do not respond to 5-azacitidine can be enrolled in this clinical trial.

Study	TEMDS-Study	Dose escalation study to Volasertib in combination with Azacitidine	VidazaAllo-Study	RELAZA2-Study	ROMDS-Study
Target	Assess the efficacy of temsirolimus	To assess the maximum tolerated dose, safety, pharmacokinetics and efficacy of Volasertib in combination with Azacitidine	Comparison of Azacitidine vs. Azacitidine followed by stem cell transplantation	Assess the efficacy of azacitidine in case of imminent relapse after transplantation (MRD-positive but no hematologic remission)	Assess the efficacy of azacitidine in combination with romidepsin
Target group	Patients with azacitidine intolerance or resistance	Previously untreated patients (IPSS-HIGH and CMML), are not suitable for intensive therapy	Patients (IPSS INT2 / HIGH) aged 55-70 years who are qualify for allogeneic stem cell transplantation	Patients after successful allogeneic stem cell transplantation	Patients with an inadequate response to azacitidine or patients who are not qualify for allogeneic stem cell transplantation
Phase	Phase II	Phase I	Phase II	Phase II	Phase I

Figure 2: Overview studies Higher risk MDS according to IPSS

Non-interventional trials in MDS

A non-interventional trial for MDS patients undergoing allogeneic transplantation is the ALLIVE trial, which evaluates the role of iron overload in the outcome of allogeneic transplantation. Patients are assessed for iron content by liver MRI imaging before and after transplant as well as by measurement of labile plasma iron and serum ferritin levels.

For further information on which MDS centers in Germany are currently enrolling patients as well as more detailed information on specific trials please contact EMSCO at

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Current MDS trials of the French group myelodysplasia (GFM) in France

Ongoing trials

Higher risk - First line

GFM-AZA intensive: A phase I/II study of the efficacy and safety of an intensified schedule of azacitidine (Vidaza®) in intermediate-2 and high risk MDS patients. Planned for 81 patients.

GFM-ExVD-AZA: A phase I/II study of the combination of deferasirox-vitamin D and azacitidine in high-risk MDS (IPSS INT-2 and HIGH). Planned for 50 patients.

GFM-Aza-Ida-09: A phase I-II study of the efficacy and safety of Idarubicin combined to azacitidine in int-2 or high risk MDS. Planned for 41 patients. Inclusion almost finished.

Higher risk - Second line (after AZA failure)

GFM-Aza-Vor: Addition of suberoylanilide hydroxamic acid (Vorinostat) to azacitidine in patients with higher risk MDS resistant to AZA alone. A phase II add-on study in patients with azacitidine failure. Planned for 48 patients.

GFM-Acadésine: A phase I-II trial of acadesine in IPSS high and int 2 myelodysplastic syndromes, AML with 20-30% marrow blasts and CMML type 2 not responding to azacitidine or decitabine for at least 6 courses or relapsing after a response. Planned for 30 patients minimum.

Higher risk MDS with del(5q)- First line

GFM-AZA-REV: A phase II study of the efficacy and safety of lenalidomide combined to 5-azacytidine in intermediate-2 or high risk MDS and AML with del(5q). Planned for 49 patients. Inclusion finished.

Figure 3

List of trials that will open soon

Lower risk MDS with del(5q)

Sintra-Rev: Multicenter, randomized, double-blind, phase III study of Revlimid® (lenalidomide) versus placebo in patients with low risk MDS (low and intermediate-1 IPSS) with alteration in 5q and anemia without the need of transfusion. In cooperation with the Spanish MDS group (GESMD).

Lower risk MDS with thrombocytopenia

Eltrombopag for the treatment of thrombocytopenia due to low- and intermediate risk MDS. In cooperation with the Italian GIMEMA MDS group.

Higher risk - Second line (after AZA failure)

GFM-Aza-LDE: A single-arm dose-finding phase Ib multicenter study of the oral smoothened antagonist LDE225 in combination with azacitidine for high risk patients with MDS patients having failed AZA alone.

Figure 4

CMML

GFM-LMMC-Eltrombopag: A Phase I/II study of eltrombopag in patients with CMML and thrombocytopenia.

GFM-DAC-LMMCA: Randomized Phase III study of decitabine and hydroxyurea in patients with advanced proliferative CMML. In cooperation with the German and Italian MDS groups.

Planned trials

Lower risk MDS with del(5q)

AVATAR–STUDY: Molecular risk-guided treatment comparing lenalidomide versus azacitidine plus lenalidomide in lenalidomide-naive del(5q) MDS harboring a TP53 mutation. In cooperation with the German MDS group.

Higher risk - Second line (after AZA failure)

SGI-110–STUDY: A phase II trial of SGI-110 in patients with IPSS high and int 2 MDS, AML with 20-30% marrow blasts and CMML type 2 not responding to azacitidine or decitabine after at least 6 courses or relapsing after a response.

Autor: Prof. P. Fenaux

Rapid access to information through a network of researchers: 7th MDS Colloquium in March in Berlin

For many years now, researchers have been concentrating on the complex group of myelodysplastic syndromes (MDS). Productive cooperations are continuously being formed between various universities and research institutions, both nationally and internationally. Ideas are exchanged, strengths are focussed and potentials are merged, thereby creating a forum in which knowledge can be generated in a more comprehensive and effective way. The dedicated scientists within this MDS network have been successfully able to characterize this condition even more precisely and to optimize treatment options. Therapeutic possibilities that are available today are able to ease the symptoms of MDS and to significantly improve the quality of life of the patients. To date, a cure for MDS is only possible through stem cell transplantation.

On 28 and 29 March 2014, the Association for Medical Innovation – Haematology and Oncology mbH (GMIHO) invites you to the 7th MDS Colloquium in Berlin. Sponsored by Celgene, the conference functions as a platform for exchanging research result as well as discussions of selected clinical cases, and is meant to motivate and inspire future studies.

Renowned lecturers working at various universities throughout Europe and the USA will present their findings and their innovative approaches, while reporting on their unique experiences.

Figure 5: Skyline of Berlin

The following topics, among others, will be addressed at the colloquium:

- Molecular aberrations in MDS and AML - any commonalities?
- How to manage cytopenia in low-risk MDS?
- Treatment of MDS and AML patients with demethylating agents. Why, which drug, which patient and how long?
- Which MDS patients should not be transplanted?
- Interactive clinical case: Is there a role of iron chelation in higher-risk MDS?
- What to do in high-risk MDS and AML when conventional therapy fails?

At the end of each lecture block there will be time for questions and discussions. This way, all participants have the opportunity to take part and to actively help shape the congress.

The complete programme as well as information about the lecturers and the event in general is available at **www.mds-colloquium.de**.

The 7th MDS Colloquium is supported by

Celgene

Author: F. Manthei

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

After a successful 2nd French-German MDS Workshop last year in Paris we are pleased to welcome you this year in Dresden on the 10th and 11th September. Again, the multiple diagnostic as well as therapeutic challenges relating to the myelodysplastic syndromes (MDS) will be in the focus of this 3rd French-German MDS Workshop. The workshop provides a unique platform for cross-border discussions between the two European study groups and it will allow to strengthen already existing and create new synergies as well as to broaden the so far very successful collaboration between the two countries in the field of clinical MDS research.

In the context of the workshop the 2nd Annual EMSCO meeting will take place – tying in with last year's tradition where the EMSCO-Kick-Off was held in Paris.

This year we will welcome you in the heart of the city in the NH Hotel Dresden Altmarkt and we are very much looking forward to an interesting event and animated discussions.

Author: S. Gloaguen

Figure 6

Overview of event recommendations

7th MDS Colloquium featuring MPN
28th to 29th March 2014 | Berlin

4th Radebeuler Hämatologicum 2014
16th to 17th May 2014 | Radebeul near Dresden

10th Congress of the French MDS study group (GFM)
22nd to 23rd May 2014 | Avignon, France

3rd French-German MDS Workshop / 2nd Annual EMSCO-Meeting
10th to 11th September 2014 | Dresden

Study meeting of the Deutsch-Österreichisch-Schweizer MDS work group DACH
September 2014 | Düsseldorf

The structure of the study coordinating office EMSCO (European Myelodysplastic Syndrome Coordinating Office) is supported by Baxter