MDS Newsletter

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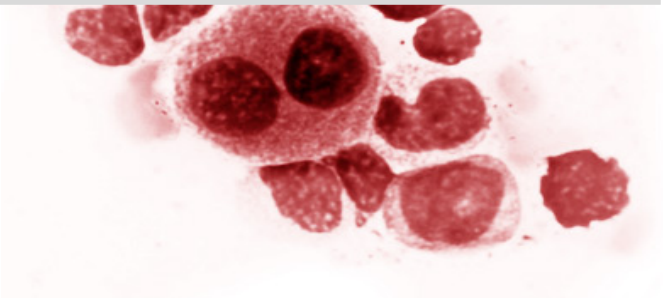
EMSCO
MYELODYSPLASTIC SYNDROMES



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.

Kind regards,

Silke Gloaguen in the name of the EMSCO team

4th Annual EMSCO Meeting in Florence on the 29th and 30th Sept. 2016

For the fourth time EMSCO has reunited specialists from all over EUROPE to discuss the latest developments in MDS diagnosis, therapy as well as current and future clinical research topics. This year, the venue took place in Florence, Italy hosted by Prof. Valeria Santini. More than 100 participants were welcomed in the beautiful premises of the Aula Magna at the Università degli Studi di Firenze.

The first day of the conference started with the EMSCO trial update. The already established and running DACOTA and EUROPE trials presented their respective updates. Furthermore two new projects were introduced: The SAMBA trial, which is testing an anti CD 123 in high-risk MDS and AML patients refractory to HMAs or having experienced a relapse on such agent.

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EMSCO conference delegates in the Aula Magna of Florence University

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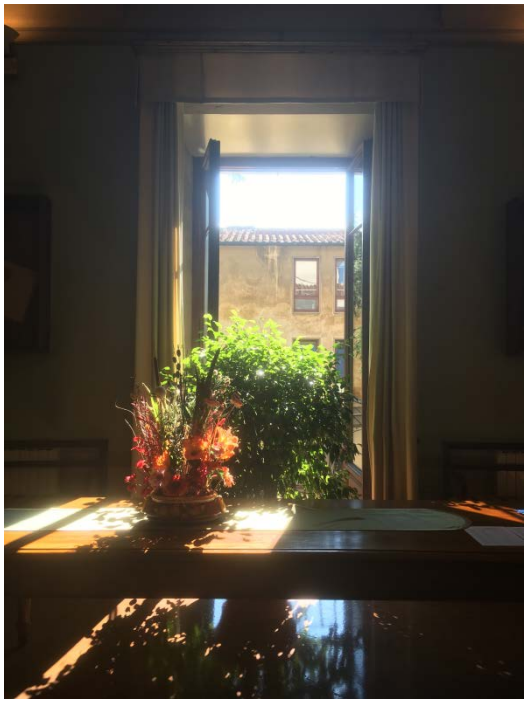
This trial is a common undertaking of the French and German study groups. The second new trial presented is the so-called VARAP study. The primary objective of the VARAP trial will be to determine the safety and tolerability of escalating doses of vosaroxin in combination with azacitidine in patients with high-risk MDS refractory to HMAs or having experienced a relapse. Furthermore snapshots of clinical trials in other European countries were provided.

The second meeting day was all about clinical and translational research. For instance, potential new outcome markers were investigated, translational options presented and in the last session biology, diagnosis, prognosis and a proposal for a new classification in CMML were discussed.

We are now looking forward to next year's meeting, which will be held in Amsterdam and will be hosted by Prof. Arjan van de Loosdrecht. Last but not least a big thank you for the successful outcome of this year's event goes to all organisers, speakers and participants as well as our supporters Celgene, Novartis, Janssen, Boehringer-Ingelheim, Onconova and Sunesis.



Foyer of the Aula Magna of Florence University

Author: Silke Gloaguen

The 4th Annual EMSCO Meeting was supported by:

The VARAP trial – a single-arm dose-finding phase I-II multicenter study of vosaroxin in combination with azacitidine for higher risk myelodysplastic syndrome patients after primary or secondary AZA failure

In higher risk MDS, after the results of CALGB randomized phase III study (CALGB 9221) comparing AZA with best supportive care, a phase III, international, multicenter, randomized, trial, (AZA 001 trial) demonstrated a survival benefit of AZA over conventional care regimen (CCR). AZA showed a median Kaplan-Meier overall survival time of 24.4 months versus 15 months with CCR. This trial was the first clinical study to demonstrate that treatment with azacitidine - as compared to CCR - can alter the natural disease course and obtain a significant OS advantage in higher risk MDS. It led to approval of AZA for the first-line treatment of higher risk MDS by EMEA in early 2009. Nevertheless, only 50 to 60% of the patients respond to AZA, and most responders relapse within 12 to 15 months resulting in a median survival of only about 6 months in these patients. As a result, there is a need for new therapies in patients who fail to respond to AZA and for whom there is currently no establish treatment.

Vosaroxin is a first-in-class anticancer quinolone derivative that targets actively replicating cells by intercalating DNA and inhibiting topoisomerase II, therefore inducing site-selective DNA double-strand breaks that result in G2 arrest and cell death through apoptosis. The major advantage of Vosaroxin over other cytotoxic agents, is that its activity is independent of p53, a common drug resistance pathway in patients with MDS or AML. In the recent randomized Phase III VALOR trial, in patients with first relapsed or refractory acute myeloid leukemia comparing HDAC with or without Vosaroxin, a significant benefit in CR rate (30.1% vs. 16.3%) was observed in the Vosaroxin arm. In that study, patients were randomly assigned to receive cytarabine (1 g/m2 intravenously on days 1–5) combined with vosaroxin (90 mg/m2 intravenously on days 1 and 4 in a first cycle; 70 mg/m2 in subsequent cycles) or placebo. As expected, Grade 3 or worse adverse events that were more frequent in the vosaroxin plus cytarabine group than in the placebo plus cytarabine group. These grade 3 events were: febrile neutropenia (47% vs 33%), stomatitis (15% vs 3%), sepsis (12% vs 5%), and pneumonia (11% vs 7%).

Moreover, in vitro studies suggest that vosaroxin in combination with azacitidine, has an additive effect on HL-60 cell line.

Based on these results, we hypothesize that vosaroxin may improve the activity of azacitidine in patients with higher risk MDS having failed (primary or secondary) azacitidine.

Two recent studies combining vosaroxin and hypomethylating agent were presented at last ASH meeting (2015). The first phase I/II study combined vosaroxin and decitabine in newly diagnosed older patients with acute myeloid leukemia or high risk MDS. 56 patients (50 AML, 6 high-risk MDS) with a median age of 69 years (range, 60 - 78) have been enrolled. In the phase I part of the study the first six patients received vosaroxin 90 mg/m2 daily on days 1 and 4 with decitabine 20 mg/m2 daily for 5 days repeated in approximately 4 to 5-week intervals for up to 7 cycles. This dose was well tolerated in the 6 patients. However, due to occurrence of 8 episodes of grade 3/4 mucositis in 7 of the subsequent 16 patients the induction dose of vosaroxin was reduced to 70 mg/m2 with the vosaroxin dose maintained at 70 mg/m2 or reduced to 50 mg/m2 in consolidation cycles. All 56 pts have completed >=2 cycles of therapy and were evaluable for response; 30 (54%) achieved CR, 8 (14%) CRp, and 5 (9%) CRi for an overall response rate of 77%. Of note, 55% of the patients with TP53 mutation achieved CR and 42% of the patients with unfavorable karytotpye, suggesting that response to Vosaroxin could be observed irrespective to the baseline cytogenetic. In the second one21, vosaroxin was combined to azacitidine for the 1st line treatement of MDS.

Vosaroxin was administered on days 1 and 4, and azacitidine on days 1-7 of a 28 day cycle. The MTD of vosaroxin combined with azacitidine was 34 mg/m2 /day when given on days 1 and 4 with a fixed dose of 75 mg/m2 of azacitidine on days 1-7. Overall, even if the number of patients was limited (n=12), the response rate was encouraging with 67% of mCR/mCR with HI.

We plan to study the efficacy of azacitidine and Vosaroxin in two differents groups of patients with higher risk MDS:

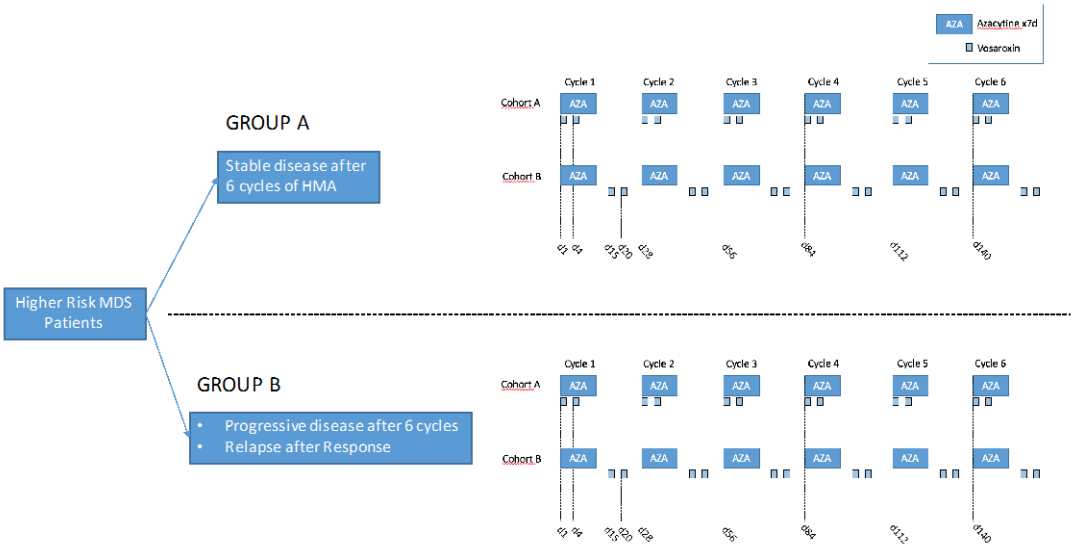
- **Group A:** Patients with higher risk MDS and who failed to achieved any type of response after 6 cycles of AZA (stable disease)
- **Group B:** Patients with higher risk MDS and who had disease progression either after 6 cycles of AZA (primary resistant) or after achieving initial response to aza and had subsequently relapsed (secondary resistance)

Given the toxicity profile of the two drugs, we will test, in an escalated dosing trial, two different combinations of the drug with azacitidine:

- **In the first cohort**, we will test escalating dose (starting at 30 mg/m2) of vosaroxin given at days 1 and 4 of each cycle
- **In the second cohort**, we will test escalating dose (starting at 30 mg/m2) of vosaroxin given at days 15 and 20 of each cycle

The primary objective of the study will be to determine the safety and tolerability of escalating doses of vosaroxin in combination with azacitidine in patients with high-risk MDS without response after at least 6 cycles of azacitidine or decitabine or relapsing after a response (but without overt progression, i.e. AML progression if patients had no AML at onset of azacitidine/decitabine, or doubling of marrow blast percentage between onset of azacitidine/decitabine and screening).

Design of the VARAP trial:



Author: Lionel Adès

15th Annual D-A-CH MDS Meeting in Düsseldorf on the 14th Sept. 2016

On the 14th of September 2016 the 15th annual D-A-CH MDS Meeting took place in Düsseldorf hosted by Prof. Ulrich Germing. The purpose of this yearly reunion is to foster and further expand collaborative projects between the three countries and to discuss current and potential future projects initiated in this cross-border context.

As every year, about 50 collaborators gathered in Düsseldorf to exchange ideas. During the first part of the day, various common initiatives presented an overview regarding their current status, the current biobanking update was presented, the running EMSCO projects discussed and a report on this year's consensus meeting on MDS diagnosis was given.

The second part of the meeting was filled with scientific contributions on pathophysiology, diagnosis, molecular genetics and prognosis. In this context, first of all registries and prognostic topics were discussed. Furthermore, studies with a molecular focus were presented, for instance an individual risk prediction tool for bone marrow transplant patients by Michael Heuser from Hannover and an analysis of epigenetic and genetic changes during MDS progression by Sandra Pohl from Regensburg.

Prof. Ulrich Germing, host of the 15th Annual D-A-CH MDS Meeting in Düsseldorf

Julie Schanz from Göttingen talked about rare chromosomal aberrations, Christina Ganster from the same hospital focused on the loss of the Y chromosome and Judith Neukirchen from Düsseldorf presented some new evidence on clonal evolution in MDS. Finally, the last block of the meeting focused on diagnostics and specifically on erythropoiesis of del(5q) MDS and mastocytosis with an associated MDS.

Overall, the D-A-CH MDS community produced 17 common publications between September 2015 and September 2016 and Prof. Germing is now looking forward to another productive year ahead.

Author: Silke Gloaguen

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