Newsletter Issue 21
November 2018

Contents

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1. Message from the Chair

Welcome to the November 2018 EUMDS newsletter

The registry is well on its way to the next milestone of 2,500 patients. Currently, 2462 patients from 17 countries and 146 centres have been included. We are glad to announce that Switzerland has joined the EUMDS Registry. In this newsletter Nicolas Bonadies – PI for Switzerland - describes the innovative approach in Switzerland to organise data collection in MDS at a national level in collaboration with the national health organisations, including SAKK. The Swiss registry has adapted their CRF to the EUMDS format, which will facilitate electronic transmission of the data from the Swiss national registry to the European registry.

Numerous research questions are being addressed in the various sub studies of the Registry, and the number of published studies in 2018 has further increased to five: the LPI study, the metaphases study, the first quality of life study, the platelet kinetics study, and the immunosuppressive treatment study (a collaboration with a USA consortium).

Moreover, four abstracts have been submitted to the ASH 2018 meeting, and all have been accepted for poster presentation. An overview of the publications 2018 and the posters at ASH is provided in this newsletter. Many other studies are underway. On October 2nd, we submitted a stage 1 application for our SMART study: 'Shared causative mechanisms in MDS and Ageing-RelaTed co-morbidities' to the Horizon 2020 programme. In this Newsletter you will find a summary of this new project.

The progress of the EUMDS and MDS-RIGHT projects will be presented and discussed during our planned meetings: MDS-RIGHT Scientific meeting, Amsterdam (Schiphol), October 25-26, 2018; ELN meeting at ASH, San Diego, December 2, 2018; the EUMDS/MDS-RIGHT meeting in Mannheim February 11-12, 2019; and the EUMDS/MDS-RIGHT meeting in Copenhagen May 8, 2019. We welcome all of you to join the meetings in San Diego and Mannheim, and meet your colleagues within the EUMDS Registry.

Theo de Witte
EUMDS Chair

2. I-CARE for MDS

Impact of guideline adherence on effectiveness and safety of health CARE provided to MDS patients (SAKK 33/18)

Nicolas Bonadies*, Julia Bohlius & Georg Stüssi
(SAKK and Swiss MDS Study Group and *new PI EUMDS registry)

The Swiss MDS Study Group (SMSG) started collecting prospective data and samples of MDS patients in a structured research network, the Swiss MDS Registry/Biobank platform, in 2016. This initiative was motivated by the emerging impact of MDS on healthcare resources, the limited availability of relevant population-based data and the increasing heterogeneity of the disease. In collaboration with national and international partners from the European Leukemia Net (ELN), this platform shall enable continuous recruitment of patients for health-service, clinical, translational and basic science research projects, aiming for the implementation of personalized and precision medicine in MDS patients.

The I-CARE for MDS project is the first multicenter study performed on this platform. This observational study will investigate the impact of guideline adherence on effectiveness and safety of health-care provided to MDS patients. The objectives of the study are:

1. development of guideline-based indicators (GBIs) for the dimensions of diagnostics/risk-stratification, treatment and provider/ institutional characteristics;
2. assessment of the level of adherence/non-adherence for each GBI as well as patient, disease and provider characteristics associated with non-adherence;
3. evaluation of the impact of GBI adherence on relevant primary (QoL, hospitalisation, bleeding, infections, cardiovascular events/t hrombosis) and secondary outcomes (PFS, LFS and OS).

The sponsorship, coordination and logistic support of I-CARE for MDS was taken over by the Swiss Group for Clinical Cancer Research (SAKK 33/18) in May 2018 and the national/international extension of the study is planned for Q1/2019. International experts have been appointed for rating candidate GBIs proposed by the study group within two rounds of a modified RAND technique, a specific form of a DELPHI process. These GBIs will represent a tool for measurement of guideline adherence and may be suitable as a general instrument for the measurement of quality of care in MDS. The collaboration with EUMDS will allow expanding the research question to the European level and will enable the identification of small effects at patient as well as institutional level. The study will help to measure and define quality of care, identify shortcomings and finally formulate recommendations to improve care of MDS patients.

3. SMART proposal

SMART is a potential new sub study within the EUMDS Registry. A dedicated working group consisting of participants from the EUMDS registry, MDS WorkPackage (WP8) of the European LeukemiaNet (founding organisation of EUMDS), the MDS-RIGHT project, and experts from several other specialisms, has been working on a proposal for the Horizo2020 call 'Better health and care, economic growth and sustainable health systems'. The topic title of the specific programme is 'understanding causative mechanisms in co- and multimorbidities'

Both myelodysplastic syndromes and clonal haematopoeisis of unknown potential are associated with many chronic co-morbidities in the ageing population. They seem to influence one another through common pathways of clonal haematopoeisis, inflammation, immune dysregulation and ageing. The interaction of these causative mechanisms remains largely unknown. SMART aims to shed light into these underlying causative mechanisms (and their interaction) of MDS and several co-morbidities.

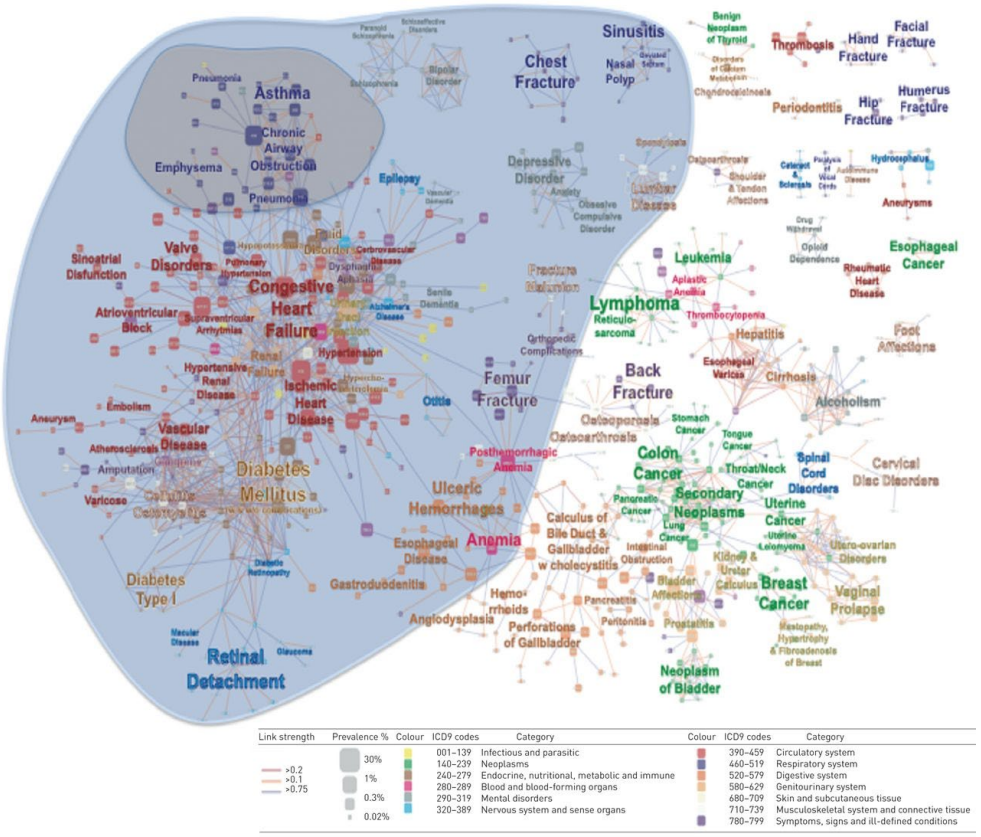


Image taken from Divo, Martinez & Mannino; European Respiratory Journal 2014 44: 1055-1068

4. Study in the spotlight: Prognostic impact of red blood cell transfusion dose density

Red blood cell transfusions (transfusions) remain the major component of the supportive care of patients with myelodysplastic syndromes (MDS). Patients receiving less than 1 transfusion unit per month regularly are defined as transfusion independent. However, we hypothesized that also these patients may suffer from deleterious effects of transfusion. In this study we addressed several statistical challenges by using proportional hazards regression with time-varying covariates. We calculated the transfusion rate at each reported visit during all preceding visit intervals from the date of the first reported transfusion. This was defined as dose density, which reflects an average rate of receiving transfusions during the whole observation period until the date of the last visit during the last interval at that time point.

Of the 1267 patients included in the analyses, 317 patients had died and in 162 patients the disease had progressed. Transfusion dose density was inversely associated with progression-free survival ($p < 1x104$): dose density had an increasing effect on hazard until a dose density of about 1 unit per month (figure 1a,b). After correction for three relevant therapeutic interventions (erythropoietin stimulating agents, lenalidomide and iron chelation) the dose density effect continues to increase beyond 2 RBC units per month (figure 1c).

Overall, the negative effect of transfusions on progression-free survival already occurs at low transfusion densities below 1 unit per month. This indicates that transfusion dependency, even at relatively low dose densities, may be considered as an indicator of inferior survival.

This manuscript will be submitted for publication to Haematologica in November 2018.

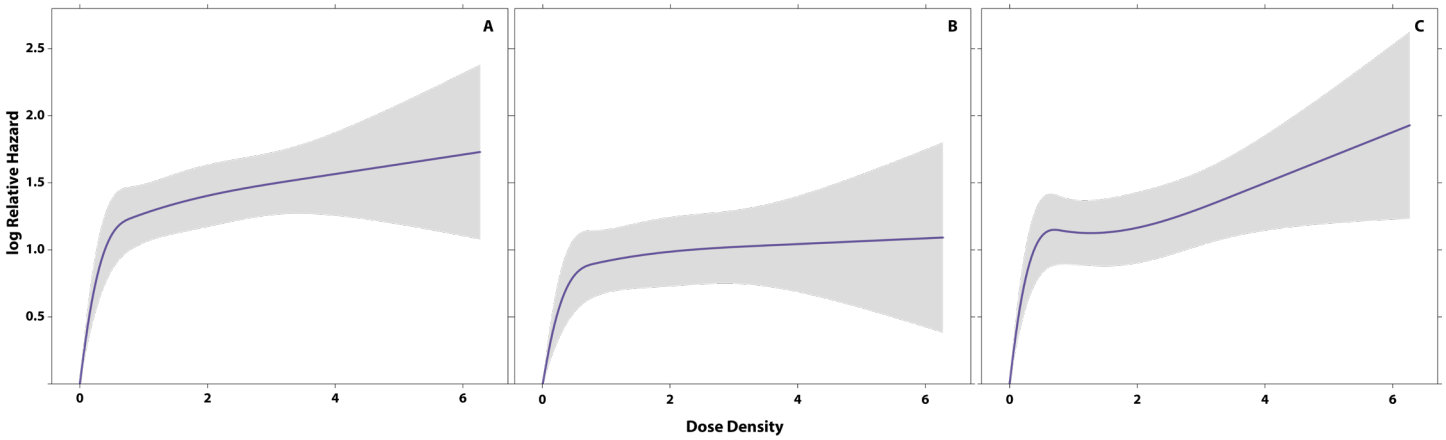


Figure 1a: Univariate analysis of influence of dose density on progression-free survival; Figure 1b: Dose density effect on progression free survival in a multivariate regression model unadjusted for the three treatment variables; Figure 1c: Dose density effect on progression free survival in a multivariate regression model adjusted for the three most common treatment interventions.

5. 2018 publications & ASH posters

In addition to the Demographics (2015), ESA and Cytomorphology (2017) papers, 5 more papers on EUMDS data have been published in 2018:

- de Swart L et al. Labile plasma iron levels predict survival in patients with lower-risk Myelodysplastic syndromes. Haematologica 2018 Jan;103(1):69-79 PMID: 29122992
- de Swart L et al. Prognostic impact of a suboptimal number of analyzed metaphases in normal karyotype lower-risk MDS. Leuk Res. 2018 Apr;67:21-26 PMID: 29407183
- Stauder R et al. Health-related quality of life in lower-risk MDS patients compared with age- and sex-matched reference populations: a European LeukemiaNet study. Leukemia 2018 Jun;32(6):1380-1392 PMID: 29572506
- Itzykson R et al. Early platelet count kinetics has prognostic value in lower-risk MDS. Blood Adv. 2018 Aug 28;2(16):2079-2089 PMID: 30126931
- Stahl M et al. The use of immunosuppressive therapy in MDS: clinical outcomes and their predictors in a large international patient cohort. Blood Adv. 2018 Jul 24;2(14):1765-1772 PMID: 30037803 (a collaboration with a USA consortium)

A further two manuscripts (tranfusion and iron chelation) will be submitted in November.

EUMDS poster presentations at ASH 2018

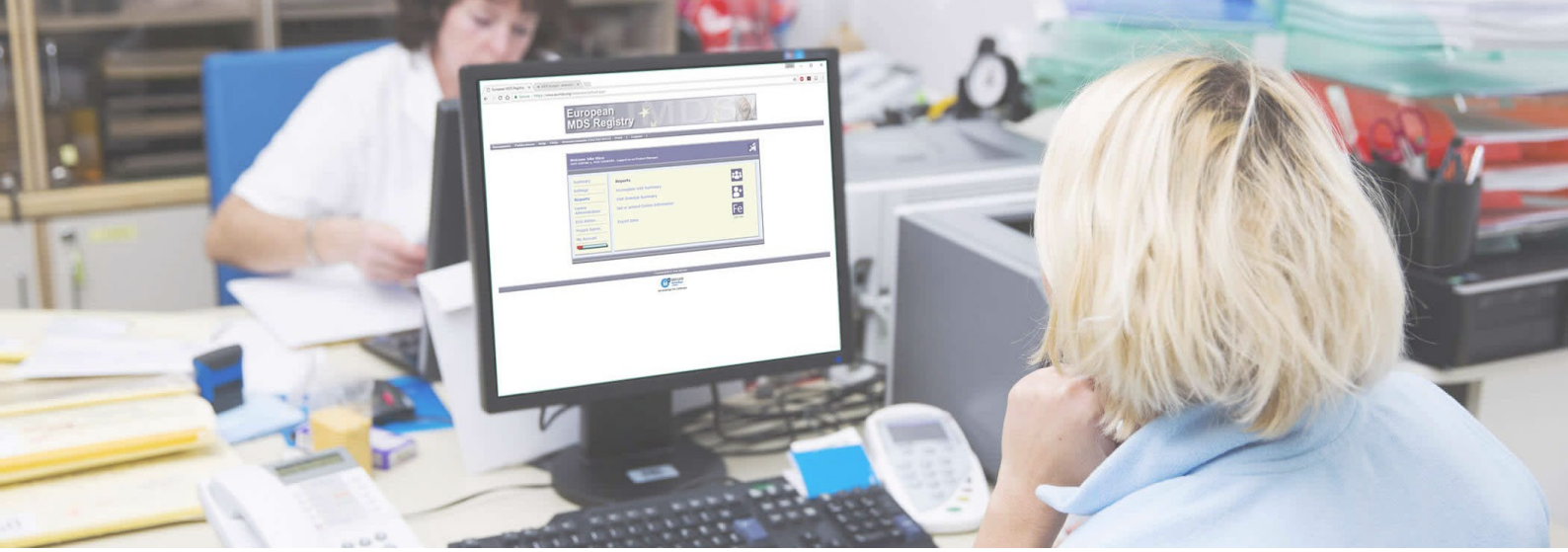
Sun 2 Dec, 6:00 - 8:00 PM, Session: 902 Health Services Research—Malignant Diseases: Poster II
#3532: HRQoL longitudinal – R. Stauder et al.

Mon 3 Dec, 6:00 - 8:00 PM, Session: 637 Myelodysplastic Syndromes—Clinical Studies: Poster III
#4357: Diagnostic Algorithm – H. Oster et al.
#4385: Causes of Death – K. Madry et al.
#4392: Iron sub study 2 (LPI) – M. Hoeks et al.

Furthermore, there is a poster on the MDS-RIGHT activities on Sat 1 Dec, 6:15 - 8:15 PM Session: 904 Outcomes Research—Malignant Conditions: Poster I
#2295: MDS-PRO – I. Stojkov et al.

Interested?

If you are interested in initiating a new sub study or if you would like to join an existing sub study, please contact the national PI of your country. If you do not have the contact details of your national PI, please contact project management: Karien.croezen@radboudumc.nl.



8. Database updates

We have recently pushed an update to all patients who did not have a protocol version set in their data. These patients are now set as protocol version 2.2.

Please remember, when you re-consent a patient, to update the protocol to version 5.1 in the Consent section of the database.

Consent

EUMDS ID:

Protocol:
Patient is recruited under protocol version: 5.1

Re-consent

- Patient renews consent for EUMDS and allows use of diagnostic samples
- Patient renews consent for EUMDS and refuses use of diagnostic samples
- Patient refuses renewed consent for EUMDS (complete withdrawal of consent section below)
- Not applicable
- Not available yet

Date of re-consent:

Unsolicited findings

- Patient wishes to be informed of unsolicited findings
- Patient does not wish to be informed of unsolicited findings
- Patient refuses consent for testing with a chance of unsolicited findings
- Not applicable (protocol 2.2)

Withdrawal

Patient continues participation in EUMDS but withdraws consent for testing with a chance of unsolicited findings

Patient withdraws consent for use of samples

Patient withdraws consent for all participation in EUMDS

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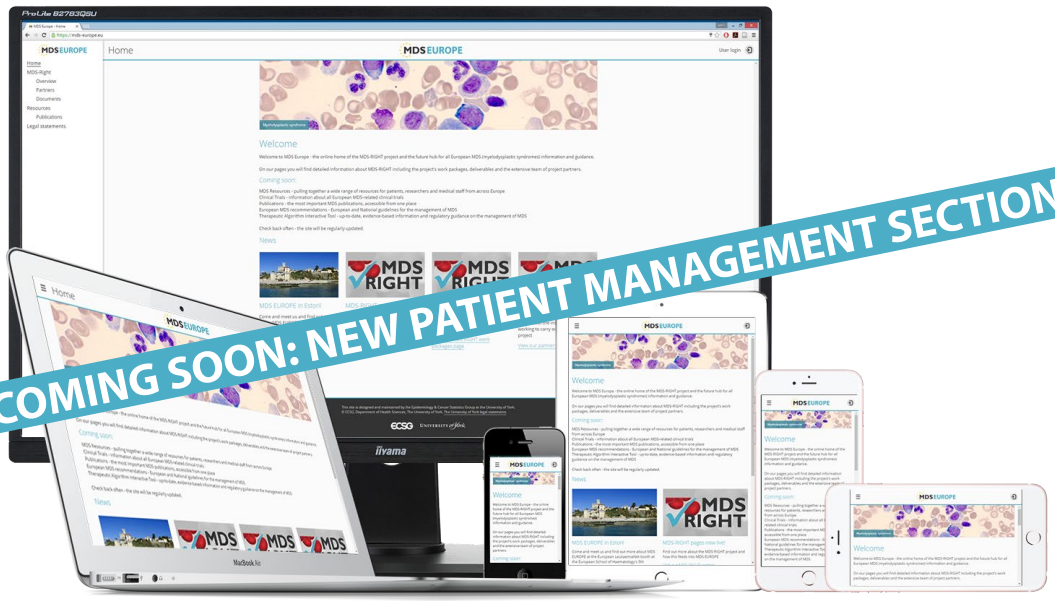

COMING SOON: NEW PATIENT MANAGEMENT SECTION