**EUMDS symposium**

**Celebrating 10 years EUMDS Registry**

Introduction and overview program

The EUMDS registry is celebrating its 10th anniversary: from the beginning, 10 years ago, the EUMDS registry has collected a great variety of data of over 2500 MDS patients in cooperation with more than 150 sites across Europe. During this symposium both international and national EUMDS investigators will look back to the past 10 years and will share the results obtained so far. We will also look at the future: what are our ambitions for the EUMDS registry for the years ahead?

The international prognostic scoring systems (IPSS and IPSS-Revised) have well established short and medium-term prognosis in MDS, but long-term prognostic indicators (PI) in lower-risk MDS (LR-MDS), largely predominating in elderly patients who often have comorbidities, are less well known. The EUMDS Registry explored longitudinally new PI, other than those integrated in the IPSS-R, such as red blood cell transfusion (RBCT) dependency, RBCT dose density, Health-related Quality of Life (HRQoL), and platelet decline over time and labile plasma iron (LPI). Moreover, most LR-MDS patients die from causes, frequently present in elderly individuals, but indirectly related to MDS.

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PROGRAM:

09:00-09:30: *Registration, coffee*

09:30-09:35: Welcome and opening – Theo de Witte (NL)

09:35-9:45: Ten years EUMDS: an overview – David Bowen (UK)

9:45-10:00 Optimization of ESA treatment in LR-MDS – Eva Hellström-Lindbergh (SW)

10:00:10:15: Causes of death in LR-MDS patients – Krysztof Madry (PL)

10:15-10:30: Non-invasive diagnostic algorithm – Moshe Mittelman (IL)

10:30-10:45: Kinetics of cytopenias – Raphael Itzykson (FR)

10:45-11:15: *Coffee break – ground floor*

11:15-11:30: Longitudinal Health-related Quality of Life in MDS patients – Reinhard Stauder (AU)

11:30-11:45: Transfusions and iron toxicity – Louise de Swart (NL)

11:45-12:00: Iron chelation – Marlijn Hoeks (NL)

12:00-12:15: General implementation EUMDS in the Netherlands – Saskia Langemeijer

12:15-12:30: Future of EUMDS and closure – Saskia Langemeijer

12:30-14:00: *Lunch*

Location:

Auditorium Radboud University

Comeniuslaan 2

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Background Speakers & Scientific Topics:

*10 years EUMDS: an overview; speaker: Dr David Bowen, senior lecturer, St. James's Institute of Oncology, Leeds Teaching Hospitals, Leeds, United Kingdom*

The international prognostic scoring systems (IPSS and IPSS-Revised) have well established short and medium-term prognosis in MDS(1) as validated by the EUMDS Registry. However, long-term prognostic indicators (PI) in lower-risk MDS (LR-MDS), largely predominating in elderly patients who often have comorbidities, are less well known. The EUMDS Registry explored longitudinally new PI, other than those integrated in the IPSS-R, such as RBC transfusion (RBCT) dependency, RBCT dose density, HRQoL, platelet decline over time and labile plasma iron (LPI). Moreover, most LR-MDS patients, die from causes, frequently present in elderly individuals, but indirectly related to MDS. Studies on additional PI, such as molecular and flow cytometry indicators, are ongoing.

*Optimization of ESA treatment in LR-MDS; speaker: Eva Hellström-Lindbergh, Department of Medicine, Division of Hematology, Karolinska Institutet, Stockholm, Sweden*

We analysed the usage and clinical impact of erythropoiesis-stimulating agents (ESAs) in 1696 patients enrolled in the EUMDS Registry between 2008 and 2014 using proportional hazards models weighting observations by propensity to receive ESA treatment within a subset of anaemic patients with or without a regular transfusion need. ESA treatment was associated with a nonsignificant survival benefit (HR 0.82, 95% CI: 0.65–1.04, P = 0.09). This benefit was larger amongst patients without prior transfusions (P = 0.07). Responding patients had a better prognosis in terms of a lower risk of death (HR 0.65, 95% CI: 0.45–0.893, P = 0.018). Appropriate use of ESAs can significantly delay the onset of a regular transfusion need in patients with LR- MDS.

*Causes of death in MDS patients, speaker: Krysztof Madry, Department of Haematology, Oncology and Internal Medicine, Warszawa Medical University, Warszawa, Poland*

Data on causes of death (COD) in patients with LR-MDS is limited and sometimes conflicting. Infections and cardiovascular disorders (CVD) have been reported as frequent COD in LR-MDS, but the question is whether the incidence is higher than in age-matched population. MDS-related complications (CVD and infections) are the most common causes of death in LR-MDS patients. Comparison of overall and relative survival indicates that excess mortality in LR-MDS patients can be mainly explained by MDS/AML related causes. Interestingly, the strongest influence of MDS/AML attributable deaths is observed during the first year since diagnosis, but this difference continues to increase to 14 years difference 10 years after diagnosis. Factors such as gender, WHO subtype, IPSS, MDS-CI and RBC transfusion dependency have relevant impact on cause of death.

*Non-invasive diagnostic algorithm, speaker: Dr Moshe Mittelman, Department of Medicine A, Tel Aviv Sourasky (Ichilov) Medical Center and Sackler Medical Faculty, Tel Aviv University, Tel Aviv, Israel*

An invasive Bone marrow (BM) investigation is usually required to diagnose and classify patients with MDS. The main aim of this study is to investigate the possibility of diagnosing MDS noninvasively in at least a relevant portion of the patients. We improved the original model to a gradient boosted model during 3 subsequent phases, increased the number of variables to 10 generally available variables and the number of patients and controls to 501 patients each. Based on this model, we could diagnose or exclude MDS in 84% of the cases. Therefore, for most patients with cytopenia of unknown origin, MDS could be diagnosed or ruled out non-invasively without a BM examination. A Web app and prospective study is planned for the near future.

*Kinetics of cytopenias, speaker: Dr Raphael Itzykson, Département d'Hématologie, Hôpital Saint-Louis, Assistance Publique des Hôpitaux de Paris (AP-HP) and Université Paris Diderot, Paris, France*

Prognosis of LR-MDS is heterogeneous and relies on steady state assessment of cytopenias. We analyzed relative drops in platelet counts during the first six months follow-up of LR-MDS 807 patients to design a non-invasive and affordable prognostic classifier relying on the dynamics of cytopenias. A relative drop in platelets >25% at the landmark predicted shorter OS (5-year OS 22% versus 49% with platelet drop ≤25%, *P*<104), regardless of baseline IPSS-R or absolute platelet counts. A classifier based on RBCT-dependency and relative platelet drop >25% at the 6 months landmark showed a 5-year OS of 53%, 33% and 9% respectively (P<0.0001) in patients with none, either or both criteria, and regardless of IPSS-R risk category. Combining relative platelet drop >25% and RBC-TD at six months from diagnosis provides a cheap and non-invasive way to predict outcome in lower-risk MDS. (2)

*Longitudinal HRQoL in MDS patients, speaker Dr. Reinhard Stauder, Dep. of Internal Medicine V (Haematology and Oncology), Innsbruck Medical University, Innsbruck, Austria*

Patient perception is relevant in individualized therapy planning for patients with MDS. Integration of HRQoL in studies and in clinical practice is essential. We demonstrated pronounced impairments in HRQoL in patients with MDS at diagnosis (3). However, longitudinal data on aspects of HRQoL in MDS are rare. We analysed in 745 patients with LR-MDS EQ‐5D and EQ‐VAS at baseline, and at 6 and 12 months after baseline. Longitudinal observations revealed a relevant decrease in HRQoL at 12 months particularly in the dimensions self‐care and usual activities. Patients of advanced age, males and those with moderate comorbidities most frequently report declines in HRQoL. Transfusion‐need and to a lesser degree low Hb levels at initial diagnosis represent relevant predictors of deterioration. In distinct subgroups improvements were observed in the dimension anxiety/depression over time. Likewise ESA‐treatment was associated with a non-significant change in HRQoL over time.

*Transfusions and iron toxicity; speaker: Louise de Swart MD, Department of Hematology, Radboud university medical center, Nijmegen, the Netherlands*

It is unclear whether regular RBCTs, defined as transfusion dose density (the cumulative dose received at the end of each interval divided by the time since the beginning of the interval in which the first transfusion was received) are an independent prognostic factor for survival in LR-MDS. Transfusion dose density of the 1267 analyzed patients was inversely associated with progression-free survival (p<1x10-4): dose density had an increasing effect on hazard until a dose density of about 1 unit per month. The transfusion dose density effect continued to increase beyond 2 units per month after correction for the impact of treatment with erythropoietin agents, lenalidomide and/or iron chelators.This indicates that transfusion dependency, even at relatively low dose densities, may be considered as an indicator of inferior progression-free survival.

*Iron chelation; speaker: Marlijn Hoeks MD, Department of Hematology, Radboud university medical center, Nijmegen, the Netherlands*

Iron overload due to RBCT is associated with morbidity and mortality in patients with LR-MDS). Many studies suggested improved overall survival (OS) after iron chelation therapy (ICT), but valid data are limited. We assessed the effect of iron chelation therapy (ICT) on survival and hematological improvement in LR-MDS patients in the EUMDS registry. We compared 224 chelated patients with a contemporary, non-chelated control group within the EUMDS registry, using a Cox proportional hazards model and a propensity-score matched model. The adjusted survival for chelated patients, was 0.50 (0.34-0.74) in the Cox model and 0.42 (0.27-0.63) in the propensity score model Hematological improvement occurred in a subset of patients, up to 31% and 23% reached an erythroid or platelet response, respectively. Our results suggest that ICT may improve survival and hematopoiesis in transfused LR-MDS patients.

1. de Swart L, Smith A, Johnston TW, Haase D, Droste J, Fenaux P, et al. Validation of the revised international prognostic scoring system (IPSS-R) in patients with lower-risk myelodysplastic syndromes: a report from the prospective European LeukaemiaNet MDS (EUMDS) registry. Br J Haematol. 2015;170(3):372-83.

2. Itzykson R, Crouch S, Travaglino E, Smith A, Symeonidis A, Hellstrom-Lindberg E, et al. Early platelet count kinetics has prognostic value in lower-risk myelodysplastic syndromes. Blood Adv. 2018;2(16):2079-89.

3. Stauder R, Yu G, Koinig KA, Bagguley T, Fenaux P, Symeonidis A, 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;32(6):1380-92.