

Minutes of WP8 MDS during the 11th Annual Meeting of the European LeukemiaNet, Tuesday, February 4th, 2014

1) Minutes

No comments

2) Report EUMDS Registry SC meeting – 11th Annual ELN meeting Mannheim, 04-02-2014

a) General overview of EU-MDS registry (Theo de Witte):

Currently, the first official output of the EUMDS registry is being generated. Louise de Swart is finalizing the paper describing the demographics and early treatment in lower risk MDS of the first 1000 patients with a median follow-up of 2.1 years. This paper includes a validation of prognostic discrimination of IPSS-R. For some patients, reclassification of MDS severity is observed. IPSS-R is slightly superior to IPSS in evaluating clinical outcome. Currently, over 1579 patients are included by 133 centres in 17 countries (January 2014). Croatia has joined the Registry and included the first patients.

b) Impact of transfusions on biology and progression:

No update

c) Impact of ESA (Hege Garelius):

Analyses on the impact of ESA treatment on transfusion patterns and overall survival are in a pre-final stage. A propensity model is used to correct for factors influencing the chance of MDS patients of being treated with ESA (e.g. age, country). No significant difference in survival is observed, but difference is seen in time to first transfusion after initiation of ESA treatment, and for responders versus non-responders. Information on Qol and cost-effectiveness should still be added.

d) Qol and impact of RBC transfusions:

No update

e) The prognostic impact of declining cytopenias:

No update

f) Progress of Iron Chelation Study with Novartis (Tom Johnston):

Issues of the use of a propensity score in observational studies are discussed. As treatments are not randomly assigned, correction for factors influencing the decision to start treatment is required, e.g. by means of a propensity model. Proper identification, definition, and selection of comparative groups is a key issue. All differences aside from the comparator need to be minimized. A weighting factor based on propensity is used in a regression model. Matched pairs analysis might be another approach, but this introduces biased effect estimates due to the low number of matched pairs within this study population. This summer a new interim analysis will be performed to assess whether sufficient numbers of chelated patients, more controls 'at risk' of receiving chelation and more events are available. Otherwise, analysis is postponed to no later than summer 2015.

g) Report on Cytomorphology review:

No update

h) Future EU-MDS Registry:

No update

3) Report of 6th ELN workshop of Flow cytometry in MDS, Munich, 31/10-2/11-2013
(Arjan van de Loosdrecht):

FCM is already included in the ELN guidelines for MDS (Blood 2013;122:2943-2964) as highly recommended diagnostic tool. It can be performed in suspected MDS based on well-defined standard criteria, either to diagnose or exclude MDS. Issues on how to report to clinicians are discussed. Activities include: Full implementation in an integrated diagnostic report; Revision of WHO-classification; Identification of prognostic subgroups in MDS and confirmation of FCM results in (dys)erythropoiesis; Validation in multicentre trials; trombocytes (in future). Furthermore, development of courses within ELN are proposed. Next FCM meeting: Vienna Oct 31-Nov 1, 2014 will focus (dys)erythropoiesis, (dys)megakaryopoiesis, and prospective multicentre studies.

4) Progress of the Trial Platform: EMSCO and discussion of planned trial(s) (Sonya Faber, Head of Business Development of EMSCO):

The organisational structure of EMSCO, their possibilities to facilitate international academic clinical research, education and consulting in MDS across Europe and the advantages (e.g. single point of contact, standardisation, and improvement in best practices) of this European platform for international MDS trials are presented. They gained external funding for financial independency, developed a website and logo, and are developing a common structure for trials. Their growing experience can help to overcome challenges (e.g. differences in costs between countries, distribution of drugs) in (new) clinical trials, will improve data quality, and in monitoring start-up and optimizing trial recruitment in MDS research in an ideal time frame. Ongoing activities include among others: European site mapping for MDS, creation of 'open source' clinical trial documents, and establishment of competency centre for MDS. If you want to reach many haematologists you can provide input for the newsletter by e-mail.

Moshe Mittelman presents an update of a phase II single arm study to determine the safety and efficacy of the combination of 5-Azacitidine and Lenalidomide in a 3-staged treatment in higher-risk MDS (Vi-Len-01) as a proposal for a new phase III study for EMSCO. At the end of February 2014 study will be closed with an inclusion of 30 patients. Safety profile is reasonable, and patients that continue treatment beyond 6 month have a high chance to respond. Involvement of EMSCO in a phase III RCT (using smaller dose, strict inclusion criteria and better outcome) is proposed as the involvement of several countries is required to reach sufficient numbers.

Discussion: There are 2 competing studies in the US of which 1 is still ongoing. Pierre Fenaux (PF) has a comparable phase II trial ongoing. Uwe Platzbecker indicates that one of the US studies compares the same trial arms versus a third arm. Proposal should be further discussed with PF.

5) Highlights from the MDS ELN guidelines (Theo de Witte, on behalf of Luca Malcovati):

ELN Guidelines for diagnosis and treatment of primary MDS in adults have been published in Blood 2013; 122:2943-64. Major issues are: Diagnostic approach; standardisation of FCM; International working Group; and treatment algorithms according to IPSS classification: Low, Intermediate-1 and combined Intermediate-2 and High. These algorithms need to be updated according to the IPSS-R in the near future. Key points include economic aspects, rigorous assessment of patient reported outcome in clinical practice, inclusion of patients in clinical trials and national and international registries, and a continuous update of the present guideline. Future plans encompass implementation of the guideline, update of recommendations, new projects (MDS/MPN, secondary MDS), and MDS SCT guidelines.

6) Progress of guidelines for allogeneic SCT in MDS (Theo de Witte):

The process of development of specific guidelines for allogeneic SCT in MDS on initiative of EBMT is presented. Consistent with the general guideline consensus will be based on literature review and scenario analysis by experts, and aims to provide recommendations for clinical practice to support appropriate choice of therapeutic interventions. A third version of the synopsis describing all topics to be addressed in scenario's has been sent to the expert panel, and a second draft of web-based scenario analyses based on 24 scenarios from ELN has been sent to the task force and expert panel. These analyses include important topics as e.g. immediate vs delayed allogeneic SCT, donor type, conditioning. Risk assessment according to IPSS-R, deletion of CMML and MDS-F, and deletion of topic dealing with issues after HSCT is proposed. Ongoing activities include a meeting this afternoon (14.00-16.00h) for which interested people are invited to join. Furthermore literature review and preparation of a manuscript and draft guidelines before summer 2014.

Discussion: Selection of experts consists of only EU experts. Inclusion of transatlantic experts might be meaningful. No objections to this proposition. TdW will invite additional experts.

7) Transcan (Joop Jansen):

Numerous genetic mutations have been identified in MDS. In most MDS patients at least 2-4 genetic mutations are found. Functional classification showed that Epigenetic regulation and Splicing factors are the most common cause of genetic dysregulation. A Transcan grant of € 917.000 has been awarded in Nov 2013 to correlate genetic events to clinical parameters in 1000 patients. The new project name is: TRIAGE-MDS. Funding is sufficient to get started. Materials will be collected and sequenced in Nijmegen, Biostatistics will be supervised by Martin Dugas, Münster, Germany. Pierre Fenaux, Reinhard Stauder will contribute the clinical data in collaboration with the EUMDS registry. Official starting date will be April 1st, 2014. Besides prospective collection of materials, possibilities for use of archived materials for DNA extraction is evaluated. Major issues considered in retrospective collection are Informed Consent and prevention of bias. The value of the EUMDS registry will advance with the introduction of the molecular analyses of the TRIAGE-MDS project.

Discussion: Is your goal to have BM? JJ: for quality of DNA extraction and logistics peripheral blood is preferred. Technically it is possible to collect DNA from whole blood, as well as serum and from unstained BM smears. All three methods need to be compared to assess whether clonal and sub-clonal DNA are the same in different materials. Goal is that BM should be golden standard in time. Not morphology but mutations will become the basis of classification of MDS.

8) Horizon 2020 (Theo de Witte and Reinhard Stauder):

Reinhard Stauder presents ideas for definition of new endpoints, since well established endpoints like overall survival might not be relevant in elderly due to competing risks of death. QoL, Global functioning, Use of health care resources and Co-morbidities are also important issues to evaluate in elderly populations. Furthermore, earlier diagnosis of MDS, e.g. (molecular) screening of anaemia in elderly will improve awareness of progression to MDS and vigilance, as well as differential diagnosis.

There are many calls within the section on Health, Demographic change and wellbeing of this program that fit the MDS population. ELN-board is planning to participate in the first round and some WPs have already made proposals. For WP8 there is no proposal yet. TdW suggests preparing a proposal for MDS activities and the registry focussing on: Advancing active and healthy ageing, QoL, new treatments, and chronic diseases in the elderly, as well as methods for earlier diagnosis. MDS-U / anaemia in elderly is seen in appr. 15% of the elderly in the general population. A majority of these people will have MDS, but diagnosis is not made because of necessity of BM. Additional funding will be used to integrate molecular analyses and assessment, validation and implementation of new endpoints. Participation in and proposals for Horizon 2020 will be further discussed today in the board of ELN. TdW will assess the most appropriate call(s) and draw up and submit a proposal on MDS.