Agenda MDS ELN WP8, Mannheim 31-01-2012

General issues
• Future of ELN MDS WP8 / EHA MDS WP          P. Fenaux
• Report activities WP8 for ELN Newsletter      All
• Cooperation with Pharma                      All

EU-MDS Registry
• Future meetings                              All
• Iron substudy                                 M. MacKenzie
• EPO - studies                                A. Smith (E. Hellström-Lindbergh)
• Diabetis Mellitus                            A. Symeonidis
• Cytopenias                                    R. Itzykson / P. Fenaux
• Quality of Life                               R. Stauder
• Proteomics                                   D. Bowen
• Cytology review                              M. MacKenzie

Translational research / biobanking:
relationship with EUMDS-Registry activities    J. Jansen (E. Hellström-Lindbergh)
GO MDS - application 7th FP EU                  T. de Witte
Platform for international studies, progress   U. Platzbecker
Flow cytometry on MDS, report Pavia meeting    A. v.d. Loosdrecht
Therapeutic guidelines                         L. Malcovati, M. Cazzola
Evidence based Guidelines for Optimal treatment of patients with lower risk Myelodysplastic Syndrome (MDS)

GO-MDS
De novo Low risk and intermediate-1 MDS patients

Current EUMDS registry 1200 subjects in 13 European countries, median follow up 18 months

Increased mortality and impaired Quality of Life due to bone marrow failure

Major impact: severe anaemia for which 3 treatment options: HGFs, transfusions and iron chelation

Aim: development and implementation of guidelines for optimal treatment of lower risk MDS
<table>
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<tr>
<th>Treatment</th>
<th>MDS patients treated (%)</th>
<th>Efficacy</th>
<th>Annual cost per patient (€)</th>
<th>ELSI</th>
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<tbody>
<tr>
<td>HGF</td>
<td>46%</td>
<td>Retrospective studies showed a survival advantage of HGF treatment: HR of 0.43 (P&lt;0.005) and HR of 0.61; p=0.002 respectively (Park et al. 2008; Jadersten et al. 2008; Casadevall et al., 2004; Ross et al. 2003). Early treatment with HGFs prolongs time to transfusion need (Park et al. 2010).</td>
<td>19.263</td>
<td>Ethical analysis must balance prognosis, survival, and quality of life with cost of treatment (Goss et al. 2006).</td>
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<td>42%</td>
<td>A regular need for blood transfusion is associated with a significantly lower probability of survival (HR of, 1.58; P = 0.005) (Cazzola et al. 2005).</td>
<td>8.158</td>
<td>Still missing</td>
</tr>
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<td>Ch</td>
<td>9% at 18 months will increase to 21% (50% of the transfusion dependent patients) at 5 year follow-up</td>
<td>A retrospective analyses by the GFM in 97 regularly transfused patients adequately treated with iron chelation showed an improved survival with a HR of 0.3 (p&lt;0.003) compared to a control group not treated with iron chelation (Rose et al. 2010).</td>
<td>12.000 (s.c.) to 24.000 (oral)</td>
<td>Though oral medication may be preferred by the patient, clinicians supervision of injectable or infusible medication may provide better compliance (Kogan et al. 2009)</td>
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Time schedule FP7 Call

Publication of call: 20 July 11
Deadline for submission of stage one proposals: 04 October 11, 08 December 11
Evaluation of stage one proposals: 2 December 11
Letter to coordinators of successful stage one proposals: 08 December 11
Invitation to submit a full stage two proposal: end-December 11
Coordinators informed of results of stage one proposals: end-December 11

Deadline for submission of stage two proposals: 08 February 2012, 17:00:00 Brussels time
Evaluation of stage two proposals: Finalised by beginning of April 2012
Coordinators informed of results of stage two proposals: April 2012
Invitation letter to successful coordinators to launch grant agreement negotiations with Commission services: April 2012
Letter to unsuccessful applicants: April 2012
Signature of first grant agreements: September 2012
Do we need an ELN based MDS studies coordinating office?

U. Platzbecker
Medizinische Klinik und Poliklinik I
Universitätsklinikum „Carl Gustav Carus“ Dresden
Advantages of an ELN MDS Studies Coordination Office

• **Goal:** to improve the quality of clinical MDS research

• **Initiate discussion on:**
  - Standardization and international cooperation
  - Exchange of relevant information regarding designed / planned / ongoing clinical trial
  - a “common arm” in randomized studies

• **Enabling:**
  - IITs within different MDS groups
  - Fast patient recruitment
  - More meaningful clinically relevant conclusions
  - Common data analyses from trials
Phase 1 (2012):

1. Agreement from ELN MDS Group that they would like to set-up an MDS Studies Coordination Office.

2. Set-up a common trial (GFM/GMDS-SG)
   - sharing biostatistician, possibly CRAs, data collection and management with the goal
   - to identify hurdles and practical problems (e.g. submission to IRB and national authorities, insurance, central randomization, monitoring etc.)
ELN MDS Studies Coordination Office

Phase 2 (2013): also depending on phase 1,

1. Final agreement to set-up an ELN MDS Studies Coordination Office
2. Decide the name and location (suggestion: “EMSCO” = European MDS Studies Coordinating Office)
3. Decide which studies e.g. Phase I/II/III/IV and countries to be involved
4. Set-up Committee to present idea to Pharma.
6. Use funding from studies to make ELN MDS Group financially independent.
Summary

1. The complexity of MDS requires better collaboration in clinical trials within the EU

2. ELN – ideal platform

3. Importance of clinical trial office

4. A stepwise set-up suggested

5. Robust infrastructure and funding is needed
Flow Cytometry in Myelodysplastic Syndromes

Arjan A. van de Loosdrecht, MD, PhD  
Theresia M. Westers, PhD  
On behalf of the ELN flowcytometry group in MDS

Department of Hematology  
VU University Medical Center  
VU-Institute of Cancer and Immunology (V-ICI)  
Cancer Center Amsterdam (CCA)  
Amsterdam, The Netherlands

Mannheim Jan 31 2012
Flow cytometric scoring system and WHO2008

Van de Loosdrecht and Westers et al., Blood, 2008
Alhan et al., unpublished data (May 18; 2011)
FCSS in MDS-RCMD is associated with worse overall survival

* P = .019

Current Activities of WP on MDS/FC

• Submission of clinical implementation document ELNet [consensus] [< March 1th]
• Focus on dysplastic erythropoiesis: a retrospective multicenter study [initiated]
• Prognostic models beyond FCSS: A retrospective multicenter study [initiated]
• Collaboration with the Dutch prospective validation study in low risk MDS [HOVON89: lenalidomide +/- Epo/G-CSF]
• 5th international flow/MDS ELN meeting q4-2012 (Amsterdam, NL)
Diagnosis and treatment of primary MDS in adults
Recommendations from the European LeukemiaNet

• First complete draft ready: 29-01-2011
• First authors: Mario Cazzola and Luca Malcovati
• First review by core authors (6): February 2012
• Second review by all co-authors (20): April 2012
• Submission Blood June 2012
Diagnosis and treatment of primary MDS in adults
Recommendations from the European LeukemiaNet

1. Introduction
2. Design and Methods
   2.1 Systematic review of the literature and synthesis of evidence
   2.2 Consensus phase
3. Diagnostics Procedures
   3.1 Morphology
   3.2 Bone marrow biopsy
   3.3 Flow cytometry immunophenotyping
   3.4 Cytogenetics
   3.5 Molecular genetics
4. Classification
5. Risk assessment
   5.1 Disease-related factors
      5.1.1 Prognostic relevance of somatic mutations
   5.2 Patient-related factors

6. Therapeutic options
   6.1 Watchful-waiting strategy
   6.2 Human Leukocyte Antigen (HLA)-typing
   6.3 Allogeneic stem cell transplantation
   6.4 Remission induction chemotherapy
   6.5 Low dose chemotherapy
   6.6 Hypomethylating agents
   6.7 Hematopoietic growth factors
   6.8 Immunomodulatory drugs
   6.9 Immunosuppressive therapy
   6.10 Red cell transfusion and iron chelation therapy

7. Discussion
Therapeutic algorithm for adult patients with primary MDS and intermediate-2 or high IPSS score

Intermediate-2 or High IPSS risk

- >65-70 yrs or poor performance status
  - Supportive care
  - <75 yrs
    - No suitable stem cell donor
      - poor risk cytogenetics
        - Hypomethylating agents
      - >10% BM blasts No poor risk cytogenetics
        - Hypomethylating agents
        - AML-like CT OR Hypomethylating agents
          - AML-like CT
            - Allo-SCT
          - Hypomethylating agents
            - Allo-SCT

- <65-70 yrs
  - Good performance status
  - Available stem cell donor
    - <10% BM blasts
      - Allo-SCT
    - >10% BM blasts
      - AML-like CT