

**MDS Work Package meeting in conjunction with the International MDS Symposium,
Nagasaki, Japan, May, 12, 2005**

Present

de Witte, Cazzola, Ganser, Bowen, Fenaux, Lübbert, Germing, Helström-Lindberg, Rüter

Session: Proposal for diagnostic guidelines in MDS

Coordinator Hellström:

General

In April 2005 an international working group has discussed morphological definitions of MDS subgroups (Portugal meeting). This discussion has continued during a full day meeting at the MDS symposium in Nagasaki. Relevant adjustments in the classification and diagnostic guidelines will be incorporated in our guidelines. Action: Germing and Hellström.

In addition, the guidelines of the MDS WP should be harmonized with the existing guidelines from the MDS Foundation.

This proposal refers to clinical trials, where extensive diagnostic assessments are being performed to be confident on inclusion. However, the guidelines embedded within LeukemiaNet should be more restricted. A balance should be reached in what appears realistic to perform for the majority of centres.

The diagnostic and prognostic procedures proposed by Hellström have been discussed in detail. Bowen will give feedback on this discussion to Hellström (see also: details below). A final draft will be circulated before EHA and will be discussed at EHA.

Details

Blood analysis

It is proposed to add some items and to leave out other items.

Bone marrow analysis

All those present, perform a biopsy in their centres.

It is proposed not to include as standard the following tests:

-Clot preparation (refers to blood smear) should not be a substitute for biopsy. It is proposed to leave out this item to prevent any confusion.

-Iron staining of BM aspirate.

-Peroxidase staining (peroxidase deficiency in granulocytes presents a prognostic factor), however this is more related to trials.

-Fish analysis: not routinely, therefore optional.

-Immunophenotyping: CD34+, aberrant differentiation markers. Optional.

Follow up of patients

Agreement is reached upon the mentioning of "regular BM analysis". Each centre will determine a frequency which is feasible to them, specially regarding stable patients.

In addition, the frequency of examinations depends on kind of trial / treatment and will be defined in the trial protocol as well. F.e. supportive care versus therapeutic intervention at disease progression (marrow blasts, cytopenia). In the latter case, regular BM analysis is recommended. Cytogenetic analysis has been added.

Session: Proposal for therapeutic guidelines in MDS

Coordinators Cazzola/Bowen

Proposal to update as a European guideline:

- Seek agreement from British Committee for Standards in Haematology
- Agreed by Executive of Italian Society of Haematology, January 2005.

Subcommittee

The following subcommittee is put together: Bowen, Cazzola, Fenaux, de Witte, **Gattermann, Ganser.**

Methodology

Three approaches to produce guidelines are being presented:

- 1) Consensus.
- 2) Consensus and systematic literature review.
- 3) Scenario based and systematic literature review (Evidence and consensus-based). This methodology will be used for the next guidelines

The Italian Society of Haematology has followed the third approach. 776 papers have been reviewed, clinical questions have been listed, ranked in order of relevance and evidence has been reviewed.

[Advisory council. Expert panel.](#)

[The evidence base is limited and level A evidence differs between Italian Society of Haematology and British Hem. Association.](#)

Ganser: Not many randomization controlled trials are being performed in MDS. This may be a problem for the level of evidence.

Although some centres cannot offer certain treatments (f.e. EPO) because their governments does not support this, the guidelines should recommend on the basis of effectiveness and not on availability.

Agreement has been reached to use the "Italian" model and to use the expertise of Barosi in the process of producing guidelines.

De Witte: Do we include therapy-related MDS in the guidelines as well? Discuss this during next meeting

Group composition

Suggestions as follows: Giovanni Barosi (Guideline expert), Mario Cazzola and Sergio Amadori (Italian Soc Haem), David Bowen and Ghulam Mufti (Brit Soc Haem), Eva Hellström-Lindberg (Sweden), Pierre Fenaux (France), Theo de Witte (Netherlands), Norbert Gattermann (Germany), Guillermo Sanz (Spain), Radana Neuvirtova (Czech Republic), Sante Tura (possible – representing Italian Society of Haematology as funding management organisation). Retrieval of evidence-base from literature by Luca Malcovati and Matteo Giovanni Della Porta (clinical research fellows, Pavia)

Authorship and target peer-reviewed journal – suggestions welcomed.

Ganser: Proposes to ask several MDS groups from outside of Europe to comment on the guidelines.

Fenaux: Hem. Societies from countries where no MDS expert groups exist, should be involved as well.

De Witte: Was external expert for Italian guidelines. The process worked well and was done completely by email.

The following external experts are being proposed:

Japanese MDS group

Alan List

Peter Greenberg

Time schedule

The first draft should be finished before the end of 2005.

Two face-to-face meetings (linked to other meetings) will be required to evaluate evidence and discuss management of hypothetical cases:

Informal meeting in Nagasaki.

Preparatory meeting in Stockholm, EHA: Cazzola will present agenda/format of first meeting and review of literature

First meeting in Pavia: September date?

Second meeting at ASH?

Fenaux: Annual update of the guidelines is required.

Funding

Proposal for a Pharma consortium to support a non-profit third party (suggest Italian Society of Haematology), which in turn reimburses participants' expenses and provides an honorarium for participation. Guidelines group remains blind to which companies have contributed and are not involved in commissioning financial support.

The steering committee decided to centralize the Pharma Consortium for all activities in the MDS WP during the Nagasaki meeting (see later).

Interface with LeukemiaNet Guidelines WP 18.

Session: MDS registry Coordinator Bowen/Bernasconi

Bowen presented a short summary of the aims of this registry and first actions to be taken (see also minutes of earlier meetings and draft proposal on MDS registry).

A proposed core dataset is discussed in detail.

Dataset from Italian MDS registry is much more minimal.

Germing: To use a very extensive dataset will not be very realistic.

Stauder: In Austria a population based MDS registry has just been started. Governmental registry will take several years.

Ho: Suggests to record type of previous cancer (lung, breast cancer) as well.

Fenau: Make links from core dataset to extra items (f.e. fibrosis grading) to be completed by centres especially interested in these items.

Agreement is reached to add dysplasia to core dataset (needed for WHO classification).

Sanz: Include as well whether samples from patient (DNA, RNA etc.) are available.

Fenau: Suggests to ask only for complex cytogenetic results the full description of cytogenetic analysis.

Haase: Add karyotype and nr. of metaphases analyzed.

Giagounidis: Different morphologists performing BM analysis will lead to different outcomes. Ideal: review of BM by a few morphologists.

De Witte: This will not be feasible. Alternatively, register only when a review by another morphologist has been performed.

Germing: Follow-up, transfusion details will be too complicated to register.

Agreement is reached upon annual follow-up.

MDS datasets in different contexts

Med A = core dataset, mandatory data (including clinical intervention named) intended for MDS registry, including population-based registries and national registries.

Med B = dataset related to diagnostic guidelines.

Med C = dataset related to clinical / translational studies.

Format study protocol

Circulate for comments: Med A, Med B, Med C.

Database structure

Structured in such a way that data from population based registries, clinical trials and national registries can be separated from each other.

De Witte: Emphasizes that datasets from these different registries should be compatible.

IT structure will be discussed with Ronald Brand, who has developed Promise (EBMT).

Sanz: Web-based import of data is very slow. Using e-mail works faster.

Agreement to establish registry in Health Informatics Centre (HIC), University of Dundee.

Bowen will make an inventory of the software system/requirements necessary for the development of the MDS database structure. This database structure should allow electronic conversion of the existing databases into the central database structure similar to the Promise EBMT structure (Ronald Brand).

Proposal to HIC Executive.

Funding

a) LeukemiaNet contribution

b) Pharma consortium

Bowen: Six pharm. companies have shown to be interested to support the registry.

De Witte: Funding for maintenance of the registry will not form a problem if we can show that we have the registry running.

Data access

To deliver epidemiological information to companies will not be a problem. However, to deliver data from individual patients will be questionable.

Fenaux: A committee should regulate access to the data for research. The steering committee may perform this role.

Haase: How to motivate peripheral hospitals to register?

Fenaux: Relate data access of a centre to the contribution to the registry of that particular centre.

Informed consent issue

De Witte: EBMT uses anonymous data. No consent is required from the patient.

Bowen: If the sample bank will be linked to the MDS registry, probably, an informed consent is required. Include the question whether the patient has signed a general consent.

The informed consent issue will be on the agenda of the EHA meeting

Interface with LeukemiaNet registries WP16.

Final datasets, IT platform and funding to be agreed during the EHA meeting.

Session: MDS trials Coordinator De Witte

Identification of MDS trial groups willing to cooperate within framework of LeukemiaNet

- 1) List groups that have been active up to now.
- 2) Identify formal representatives of groups.
- 3) Formalize interactions on trials.

It is emphasized that LeukemiaNet is not a trial group, however it represents a platform to develop trials. For each trial we have to decide who is responsible for running the trial.

Bowen: Is chair for clinical trials of National (UK) Cancer Group, Hem. Malignancies. **He will represent this group.**

The following groups have shown to be interested to participate:

- Pithema= Spanish GETHMDS group, Sanz
- Nordic MDS group, Hellström
- GFM group (Avicenne), Fenaux
- EORTC, de Witte,
- EBMT MDS subcommittee, de Witte
- German MDS study group, Aul, Ganser

Possible groups to be added:

- MDS group from Austria
- SAKK group, Switzerland
- Czech MDS group

Aims:

- 1) Comparing outcome of different trials.
- 2) Common control arm for different trials: fewer patients needed for control arm. This is an ambiguous issue and needs to be discussed further.

Identification of pharmaceutical companies active in MDS and willing to cooperate with LeukemiaNet

- Celgene
- Pharmion
- Amgen
- Roche
- Novartis
- Apotex
- Chugai
- CTI
- Genzyme, ATG (location Sangstet, Lyon,)

Everybody is asked to complete the list of pharm. companies and representatives. Agreement has been reached on the role of LeukemiaNet as intermediary between pharmaceutical companies and centers. Financial support is needed. Rules should be defined.

Bowen: proposes the idea of a pharma consortium rather than contracts with individual companies. One of the universities should set up a contract, including issues like access of companies to the data of the MDS group.

Sanz: LeukemiaNet should define Data access.

Bowen: Will present contract proposal to Hehlmann (coordinator LeukemiaNet).

Identification of (new) drugs/treatment modalities potentially interesting for treatment of MDS patients

Activities:

- 1) List of new drugs (phase I, II, III) with involved groups/scientists/pharmaceutical companies/potential translational activities.

2) Development of new protocols.

Many of us attend advisory boards of companies and task force meetings of trial groups developing protocols. It would be preferable to exchange information on new drugs.

Ganser: [This may be difficult, as sometimes you have signed that you may not exchange this information.](#)

De Witte: Explain to the company the relevance of information for other groups. If you are invited to an advisory board meeting of a company, make clear you are a representative of a trial group or of LeukemiaNet.

The aim is to join the forces of several MDS groups within LeukemiaNet, to become an interesting partner for companies to cooperate with.

Accreditation of new trials

Ganser: German structure for accreditation of new trials: A review committee (including statisticians) judges on the scientific quality of proposals for trials. German insurances look at this as well. Aims: To prevent bad trials. To prevent parallel trials. It will not inhibit national trials. To give a certificate of quality for new trials (not applicable for EBMT/EORTC trials).

Ganser: a review board for accreditation of new trials needs to be installed.

Ganser presented the background and rationale for the registration and certification of the MDS clinical trial protocols. See below:

REGISTRATION AND CERTIFICATION OF MDS TREATMENT PROTOCOLS

Why?

- Improvement of the design of clinical trials in the field of MDS
- Coordination of clinical trials - multicenter trials
- Improving the accrual of patients into clinical trials
- Hopefully reducing the financial burden by the insurance
- Allowing an external review by an expert panel which should help and accelerate the decision making by the responsible Ethical Review Board
- Accelerating EMEA approval of new drugs by improving the design of clinical trials

Who?

- Central MDS Review Board consisting of elected members from the European countries (European LeukemiaNet, EHA)

What it should not be?

- additional bureaucracy
- bottle neck for high quality clinical research
- method to create a closed shop of clinical research

Standard Operating Procedure for the Certification of MDS Treatment Protocols

(Project of the European LeukemiaNet)

1. Purpose of the Certification Process:
 - a. Registration of MDS treatment protocols (similar to clinicaltrials.gov)
 - b. GCP protocol review according to the international GCP recommendations (ICH-GCP)
 - c. Certification of the protocols which fulfil the ICH-GCP requirements
 - d. Information of the national authorities which have to approve the protocol (EU regulations)
2. Application in electronic form
3. Registration of treatment protocol
4. Formal evaluation of EU requirements
 - a. Protocol
 - b. CRF
 - c. Summary
 - d. Patient information
 - e. Patient agreement
 - f. List of participating centers
 - g. Insurance
 - h. Financial support (sponsorship etc.)
 - i. (Study must not have started.)
5. GCP Protocol Review
 - a. Internal evaluation of ICH-GCP criteria (master protocol) within 7 days
 - b. Nomination of external experts within 7 days
6. External review by 2 external experts according to standardized operating procedure within 3 weeks
 1. Scientific novelty
 2. Preclinical and clinical data
 3. Clarity of scientific question
 4. Statistics
 5. Safety of the patients
 6. Patient information
7. Evaluation of the protocol by Protocol Review Committee
8. Certification of the treatment protocol
9. Information of the Sponsor of the study
10. Evaluation of the progress of the trial including publication

This proposal will be discussed during the EHA meeting. Members of the steering committee can send their comments to Ganser before the EHA meeting.

Joint session together with AML work package

Discussion

De Witte: Proposes to exchange MDS diagnostic guidelines to the AML work package for comments. Probably we can develop guidelines for “myeloid diseases” (MDS and AML included, CML excluded).

Hellström/Lübbert will send the diagnostic guidelines to the AML WP. RAEBT should be reported as a separate entity (RAEBt/AML) within the AML WP.

Burnett: Proposes to enrol both AML and MDS patients in an AML protocol and to compare biological/disease related factors between these two groups

De Witte: MDS patients in AML studies are not being assessed properly before entering the study.

Büchner: Define shared criteria of response for AML and MDS.

De Witte: Proposes to discuss the Cheson criteria for its usefulness.

Translational projects

WT1 data MRD, interaction with MRD WP12 K. Tobal (King's College, London)

Correlation IPSS score and WT1 expression is high.

MRD monitoring tool: to follow patient response to treatment (n=10).

The same has been performed for AML patients, larger number of patients, to find additional MRD markers. Different groups use different sets of primers to quantify the transcript. The results using these different sets have been compared.

During normal BM development WT1 expression diminishes fast. In MDS (certain subsets?) WT1 expression maintains longer at a higher level.

Offer to send to different labs: primer sets, cell line dilutions, WT1 plasmid, ABL plasmid (is control). To analyse cell line dilutions and plasmid standard curves with selected sets.

WT1 has been tested as well as a prognostic marker on small number of patients.

Jansen: WT1 is expressed in many types of cancers, however high background levels are present. Is a clinical decision possible using WT1 as a marker?

Needs to be validated on larger number of patients.

Gene profiling W-K. Hofmann

Aim: To look for altered gene expression in low/high risk MDS compared to the expression of lineage specific genes during normal hematopoiesis (erythropoiesis, granulopoiesis, megakaryopoiesis).

To use gene expression profiles for diagnosis/classification and risk evaluation in MDS.

WT1 expression level is not very high in normal CD34+ cells.

Agreement: a change in expression should be (at least) a 3 fold change.

Comparison between real time PCR and gene profiling. Gene profiling is not a real quantitative assay, however, it is suitable for obtaining an impression of expression level.

Unselected BM cells deliver insufficient information on altered expression levels.

De Witte: Test also uncultured cells from patients, in addition to in vitro cultured cells.

Not every centre is capable to isolate CD34+ cells.

De Witte: Use material from CRIANT study.

MDS and assays on CD34+ cells:

Pro: Stem cell defect?

Homogeneous population

Clonal disorder?

Contra: Difficult to harvest

Difficult to culture

Low content of RNA

Proposal for organisation of sample banking Jansen

In MDS well-characterized archived material is scarce (compared to AML).
In several places local archives exist, but these differ in content.
Therefore, it is hard to combine samples from different centres for collaborative studies.

Aim: to facilitate collaborative studies.

- 1) Centralized database: property of samples remains with the participating centres.
- 2) Consensus protocols: allowing combining samples with uniform quality.
- 3) Standardize time of collection: diagnosis-CR-AML.
- 4) Cell type: bone marrow/ blood, granulocytes.
- 5) Standardize what to store: viable cells, RNA, DNA, protein (serum).
- 6) Overview of research interests (including Haferlach initiative).

A questionnaire will be sent around to make an inventory of which centre has stored what kind of samples.

De Witte: Include in MDS registry the question: "Does your centre has stored samples available for cooperation in LeukemiaNet? Ask for additional info?"

Ganser: Is it necessary to adjust the info on sample storage in the database, when samples (f.e. viable cells) have been used and will no longer be available?

Agreement is reached that this is not necessary (too complicated), databases will always be contaminated up to a certain level.

Celgene: European 5q-, non 5q- Revlimid studies K. Watters (Medical Director)

5q- study protocol

Assumptions: All patients included in national registries.
National registries will be coordinated through LeukemiaNet.
Need to identify patient confidentially, data protection laws.
Long term follow up possible for these patients.
Clinical trial registry: more extended dataset compared to national registry.

Depends on the country how long it takes from the moment that the drug has been registered until the drug is available commercially.

Oversight committee and central laboratories

Consistent and confirmed diagnosis, internationally validated.

Is a BM biopsy required?

Fenaux: Difficult to ask from this group of patients.

Watters: Will explain to the European drug administration that a reliable diagnosis can be made using a BM aspirate and cytology. He expects them to accept this.

De Witte: The committee on ethics will require the BM biopsy better explained in the protocol.

Cytology: Initial diagnosis by local labs.
European reviewer: Prof. Aul.
International validation by John Bennett (USA)

Study data safety monitoring board

More European representatives required.

Non 5q- study protocol

Include only EPO refractory subjects.

[Introduction of CRO, feasibility and site selection](#) S. Kavanagh

GFA: regulatory affairs regarding submission of protocols differ for each country. It is expected that trials will start in France, Denmark, Sweden and United Kingdom. Subsequently, Italy, Netherlands and Spain will follow.

24 centres have been contacted by the CRO, 22 centres have shown to be interested.

[CRO UK Kendle Int.](#) J. Kenelly

The final protocol will be presented Febr. 4th. An investigators meeting is planned before the next EHA meeting.

Translational research (gene profiling) in relation to 5q-Revlimid study W-K. Hofmann

Lenalidomide represents a pleiotropic molecule.

Aims:

To investigate the role of this drug in biological pathways: which genes are affected by the drug, f.e. pool of 31 genes, investigate pathways.

Response prediction at diagnosis: which subset of patients is eligible for treatment.

Labs deliver 500 ng RNA from $5 \cdot 10^6$ cells or frozen cells. Freezing protocol does not affect the results.

- 1) Take a BM aspirate a few weeks after the treatment started and store this sample.
- 2) Analysis of samples after 1 year after the study is unblinded.

A joint study proposal including Microfluid Card Technique (see below) will be prepared and sent to Celgene.

Translational research (Microfluid Card Technique) in relation to 5q-Revlimid study J. Jansen

Using 50 ng RNA, expression levels of 384 genes can be analyzed using different primers for amplification of RNA. This technique detects low expression of genes. It will be useful to combine this technique with gene profiling.

Action Items from MDS WP meeting Heidelberg, February, 1-2, 2005

Action	Coordinator	Target Date
Check whether the MDS WP (LeukemiaNet) will have shared sessions with the EHA MDS working group to avoid overlap	Fenau	April 2005
Exchange MDS diagnostic guidelines to the AML work package for comments and harmonization	Hellström/Lübbert	May 2005
MDS diagnostic guidelines , will be presented in the morphological working group meeting in April, 2005 and harmonized with the outcome of their discussions.	Germing, Mufti, Hellström	April 2005
Therapeutic guidelines: Seek agreement from British Committee for Standards in Haematology	Bowen	May 2005
Therapeutic guidelines: Prepare first draft to evaluate evidence and discuss management of hypothetical cases during EHA meeting in Stockholm.	Cazzola, Bowen	June 2005
MDS trials: 1) List groups that have been active up to now. 2) Identify formal representatives of groups. 3) List all protocols of trials by MDS study groups.	De Witte	June 2005
MDS trials: List of new drugs (phase I, II, III) with involved groups/scientists/pharmaceutical companies/potential translational activities.	Fenau	June 2005
MDS trials: Circulate for comments format for study protocols.	De Witte	May 2005
MDS trials: Ask National (UK) Cancer Group, Hem. Malignancies whether they will participate in LeukemiaNet.	Bowen	April 2005
MDS trials: Send around a proposal for accreditation of new trials	Ganser	May 2005
MDS registry: Proposal to HIC Executive	Bowen	June 2005
MDS registry: Circulate for comments Med A, Med B, Med C.	Bowen, Bernasconi, Hellström	June 2005
MDS registry: List features existing databases and work out details of IT structure which can integrate these population based databases	Bowen, Bernasconi	June 2005
MDS registry: IT structure will be discussed with Ronald Brand (EBMT)	Bowen	June 2005
Proposal for financial office in Hannover	Ganser	June 2005
Sample banking: A questionnaire will be sent around to make an inventory of which centre has stored what kind of samples.	Jansen	May 2005

Translational research related to Revlimid study: A joint study proposal including Gene Profiling and Microfluid Card Technique will be prepared and send to Celgene.	Hofmann, Jansen	May 2005
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