

MDS Work Package meeting in conjunction with the symposium of the European LeukemiaNet, Heidelberg, February, 1-2, 2005

Present

de Witte, Ganser, Bowen, Fenaux, Lübbert, Jansen, Huber, Padua, Germing, Ho, Krieger, Stauder, Heidtmann, Densinger, Malcovati, Della Porta, Hofmann, Louis, Porwit-Mac Donald, Orfao, Michaelsen, Giagounidis, Aul, Foster, Schmitt-Gräff, Sanz, Gotcheva, Kahlenberg, Gologan, Steider, Büsche, Haase, Verbeek, Watters, Mohr, Oelschlaegel, Pfeilstoecker,

Next meetings

Italy, end of February.

8th International MDS symposium, Nagasaki, May, 12-15, 2005

EHA, Stockholm, June, 2-5, 2005

Fenaux will check whether the MDS WP (LeukemiaNet) will have shared sessions with the EHA MDS working group to avoid overlap.

Joint session together with AML work package

Entry and response criteria (Lübbert, de Witte)

See attached slides.

Current combined AML/MDS trials (Burnett)

Discussion

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

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 response criteria for its usefulness.

Session: Proposal for diagnostic guidelines in MDS Coordinator Hellström

Hellström is excused, Bowen takes care for this session.

General

In April 2005 an international working group will discuss morphological definition of MDS. Germing and Mufti will participate in this group. The result of our discussion in the MDS WP on diagnostic guidelines, will be presented in the meeting in April and harmonized with the outcome of their discussions.

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 are being discussed in detail.

Follow up

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. E.g.

supportive care versus therapeutic intervention at disease progression (marrow blasts, cytopenia). In the latter case, regular BM analysis is recommended.

Session: Proposal for therapeutic guidelines in MDS Coordinator Cazzola/Bowen

Cazzola is excused, Bowen takes care for this session.

Proposal to update as a European guideline

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

Subcommittee

The following subcommittee is put together: Bowen, Cazzola, Fenaux, de Witte and a representative from Germany.

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).

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 randomized, controlled trials are being performed in MDS. This may be a problem for the level of evidence.

Although some centres can not offer certain treatments (e.g. 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, USA

Peter Greenberg, USA

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.
Formal meeting in Stockholm, EHA.

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.
This proposal is approved.

Interface with LeukemiaNet Guidelines WP 18.

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 ask whether they will participate.

The following groups have shown to be interested to participate:

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

Possibly to be added:

MDS group from Austria
SAK 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 pharm. companies and centres. Financial support is needed. Rules should be defined.

Bowen: Pharma consortium: Rather than individual companies, ask several companies for small amount of support. University sets up a contract, including issues like what kind of access to the data companies will have.

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: Will send around a proposal for accreditation of new trials. A board needs to be installed.

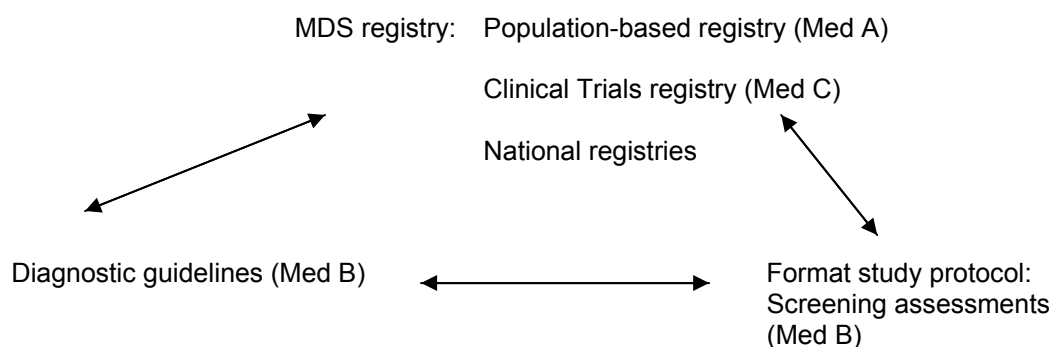
Session: MDS registry Coordinator Bowen/Bernasconi

A short summary is presented 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.

Agreement is reached upon annual follow-up.

MDS datasets in different context



Med A = core dataset, mandatory data (including clinical intervention named).

Med B = dataset related to diagnostic guidelines.

Med C = dataset related to clinical / translational studies.

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.

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

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.

Interface with LeukemiaNet registries WP16.

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

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.

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 send 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 (to 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

Dr. Watters presented the proposed 5q- Revlimid protocol. He discussed several organisational aspects of the study.

It 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.

Cytology: Initial diagnosis by local labs.
European reviewer: Prof. Aul.

International validation by John Benett (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 send 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.