European LeukemiaNet, MDS Work Package meeting, San Diego, December 3, 2004

Present

de Witte, Hellström-Lindberg, Ganser, Bowen, Fenaux, Lübbert, Cazzola, Bernasconi, Del forge, Muus, Maenpaa, Onida, Passweg, Ho, Heptinstall, Della Porta, Mallovati, Kavanagh, Bullock, O 'Neill, Mc Farlane, Kröge, Zeldis, Wattem, Pellagatti, Cermak, Mittelman

Next meetings

LeukemiaNet Annual Meeting, Heidelberg, February 1-3, 2005
Italy, end of February.
8th International MDS symposium, Nagasaki, May, 12-15, 2005
EHA, Stockholm, June, 2005

Overview of LeukemiaNet (T. de Witte)

EU funded approval Aug. 2004.
Objectives, structure and potential impact of LeukemiaNet are summarized.
Structure European LeukemiaNet:
- Disease oriented
- Central services
- Treatment research
- Diagnosis/ Follow up
- Registry/ Education

LeukemiaNet is not a trial group. It is a platform for developing trials. For each trial we have to decide who is responsible for running the trial. For example the company, Nordic MDS group or EORTC.

Organisation International MDS Registry (D. Bowen, C. Bernasconi)

Goals depend on type of data.

Population based datasets:
- Epidemiological study of subtypes of MDS combined with a catalogue of tissue bank may lead to molecular or pathological study.
  - Easy identification of samples from selected subtypes of MDS available in Biobanks)
- Derivation/Validation of new prognostic scoring systems.
  - Based on unselected patient cohorts with high quality follow up data.

Clinical trials datasets:
- Improved definition of response predictors.
- Comparison of patient selection within clinical trials to the "real world" of population-based demographics.
  - Interaction with Pharma.

National registry datasets:
- Voluntary registries exist in Italy and France. These form a good set however, they are selected.
- Already running governmental registries do not exist in Europe yet.

Quality of follow up: Sweden and Scotland have best quality of follow up registries.

Central registry set-up
University of Dundee has a very strong Health Informatics Centre, which is used to develop population-based datasets (diabetes, hypertension). They are the leading centre of Scotland for this and they have agreed to take on this project. If grant is approved, 3 to 4 months are required to get started with a programmer. Building a database is expected not to be difficult. Platforms of population-based datasets can all be easily integrated with SQL type of server, which will be used in Dundee.
1) Clinical trials: form a subgroup.
2) Population based registries: Düsseldorf, Dundee, Dijon have existing registries. Combine these existing registries.

3) National governmental registries will need more time. Scotland: starts Spring 2005. Sweden. Quality assurance programme for diagnosis is required for these registries.

Define a minimal dataset
Hellström: Which data need to be registered? Different datasets for different registries. A subcommittee needs to define a minimal dataset. No FAB. Including baseline data for registry not including all the results of the treatment. Everybody agrees.
Definition on MDS differs!! Consistent morphological diagnosis. Next year an international meeting will discuss this.

Legal issue
Guidelines for ownership and access to database need to be defined. Part of this issue will be organised centrally for the European LeukemiaNet. Dundee has a legal contact in EU who will be activated as soon the funding is secured. A EU lawyer is known who has done this already for the diabetes network. For the registries in Düsseldorf and Dundee an informed consent is obtained. Ownership of data is a legal issue, therefore a legal opinion is needed.

Sponsoring
Bowen: Funding is required for half time programmer: £ 96.000 over 3 years.
£ 4.000 LeukemiaNet (increase this?), £ 92.000 Pharma consortium (Celgene, Pharmion, Amgen, Roche, Novartis, Apotex, Chugai).
Maenpaa, Celgene: Celgene would like to receive a contract proposal including a legal opinion on what access we would have to the data.
Heptinstall, MDS foundation: Recommends to make a list of what you are offering. And recommends to state total amount of money you need, so that company can contribute.
Zeldis Celgene: In Europe you have to show pharmaco-economic benefit for each therapeutic. Burden of the disease for the community. This will be the basis for reimbursement. Registries will be useful for this.

<u>Proposal for guidelines diagnostic standards MDS</u> (E. Hellström-Lindberg)
Nordic group has defined a proposal for guidelines:
-Material and quality.
-Classifications and risk scores (FAB, WHO, IPSS).
-Definition of minimal diagnostic criteria for MDS.
-Pre-treatment variables: serum EPO-levels.

Common uniform diagnostic datasets.
Classification of cytogenetic abnormalities as prognostic factor in MDS.

Nordic guidelines are very similar to the Scottish guidelines/ datasets for registries.
Levels of evidence: Ia t/mVb.

All patients that might be candidates for therapeutic intervention in the future should have a BM analysis once a year, at least a BM biopt. Fenaux: Does not agree with a yearly BM biopt.

The Nordic guidelines can serve as a starting point for discussion, everybody is asked to deliver comments to these guidelines during the next meeting in Heidelberg.
Cazzola: You need recommendations on the proposal guidelines of about 6 experts in the field. Same procedure for therapeutic guidelines. On-line discussion and/or meetings are required.
Fenaux: Consensus of European MDS groups on guidelines is required.
Hellström: Hopes that MDS WP is representative, to define guidelines. And emphasizes to keep the procedure feasible. To fulfil all deliverables it is ineffective way of working to involve everybody in each deliverable.
De Witte: Thinks that all MDS groups are represented in MDS WP, and suggests that when the guidelines are presented on the website they can still be discussed.

Proposal for therapeutic guidelines MDS (M. Cazzola. D. Bowen)

Published Guidelines: British Society for Hematology 2003 and Italian Society for Hematology 2002. They will be updated in 2005. The German Society for Hematology has published guidelines and the Nordic group has defined guidelines as well. Cazolla will integrate these different documents.

Procedure
1) Define therapeutic tools. Evidence based efficacy.
2) Usefulness of single tools in particular patient setting.
3) How do the guidelines apply to patients.

Levels of evidence
Ia Meta analysis of randomized trials.
Ib At least one randomized clinical trial.
IIa One well designed trial without randomization.
IIb A well designed quasi experimental study.
III
IV Expert recommendation reports. They have already an expert panel to evaluate the proposal.

Hellström: what drugs are routinely available?
For example aza is not available. Revlimid in December? Discuss this further in Heidelberg.

Proposal for organisation sample banking (J. Jansen is excused)
Sample banking for exchange, translational studies and interaction with molecular WP.
Bowen: Regrets that this issue has been postponed several times.
Cell bank catalogue should get priority. Which WP is responsible for this?
Possibilities for combining data are discussed, however this is also a central issue of the LeukemiaNet.
De Witte: There will not be a central storing facility, however the information should be available on who has stored what, from which patients, with which data. This should get high priority in Heidelberg.

Gene expression profiling: proposal for MDS (W.-K. Hofmann is excused)

De Witte gives a summary of the status of this issue.
See attached slides as well.
Hofmann will prepare a proposal for micro array experiments in MDS.

Suggestions on Micro array experiments in MDS.
Aims: To use gene expression profiles for diagnosis/classification and risk evaluation in MDS.
To detect altered molecular pathways in MDS cells
To predict response to treatment?
The technique is already running for other diseases. Some preliminary data for MDS progenitor cells have been obtained.

Similar proposal for Micro fluidic cards.
Existing and future applications are summarized.
Application in MDS studies.

Interaction with other WP's

MRD WP12 (R. Padua, J. Jansen)
CMPD WP (U. Germing)
AML (M. Lübbert)

Interaction with AML WP (M. Lübbert)

See attached slides as well.

MDS and AML as a biological continuum. Separation is unnecessary and/or sometimes difficult.
Blast cut off lowered over time: 50%→30%→20%.
Cytogenetics are similar in high risk MDS and sAML, treatment related AML. Micro array data show also similar gene expression patterns for MDS and AML.
Inclusion of high risk MDS patients in AML trials.
In particular same treatments for elderly MDS and AML patients?

European, national studies recruiting both MDS and AML (according to FAB) patients.
Total number of studies> 25. /More than 25 studies in WP AML (>20% blasts).
Standard induction treatment>80% blasts.
Non-intensive treatment <20% blasts.
Studies including patients aged > 60 years: ca. 10.
Proposal: Tabulate MDS and AML studies in all countries and look for overlapping inclusion criteria.

De Witte: This assumes that groups agree that AML and MDS can be treated similar?
Bowen: sometimes small numbers form a reason for similar treatment.
De Witte: "AML like treatment in MDS is investigational treatment for most patients". This has been discussed in the meeting of MDS foundation. A group of MDS patients has been identified which do not respond to chemotherapy and SCT. This needs more attention, for this group an alternative therapy should be available.
Hellström: In MDS trials: number of blasts (FAB, RAEBt) is defined. AML trials: WHO has defined >20%blasts. Grey area, 20-30% blasts have not been identified in AML protocols. Regarding AML trials: Aim to get clear which patients are sort of MDS.
De Witte: Aim to identify patients who should not be treated in AML protocols.

Clinical trial list website (T. de Witte/E. Hellström-Lindberg)

An overview of the structure of the LeukemiaNet website is presented.
Participants are requested to complete the forms concerning information on clinical studies. In this way we can present an overview of clinical studies on MDS on the website.

Coordination of ongoing and new clinical trials
Will be discussed in Heidelberg.

Trial protocols: general issues
Ganser: No progress has been made on accreditation new trials, new drug evaluation, trial availability.
De Witte: LeukemiaNet is platform for negotiation with industry. Work package can offer structure, expertise, data from other trials.
Bowen: "Implementation of networking instruments such as upfront randomisation and common standard arm". Is there anybody who can takeover this issue?
Ganser: German statisticians/ AML study group takes care for this?
De Witte: Aim is to use the same control arm for several phase II trials. In this way less patients are required for the control arm.

Finances LeukemiaNet (T. de Witte)

Budget assignments July 2004.
25% annual symposium
25% infrastructure WP1,2,3,17
50% for WP 4-16,18
    900.000 euros per year for all groups.
    1 person month=715 euro (20-25% contribution by community).

Proposal for budget assignments august 2004.

	Reimbursement	**Annual costs**
Travel costs meetings	Reimbursement via NMC	10,000
Meeting costs	Budget WP 8 Witte/NMC	5,000
Secretariat Nijmegen	Budget WP8	9,000
Coordination Nijmegen	Budget WP8	12,000
Protocol guidelines	MDS steering committee	8,000
Diagnostic guidelines	MDS steering committee	8,000
Therapeutic guidelines	MDS steering committee	8,000
Trial list Website	MDS steering committee	8,000
International MDS registry	MDS steering committee	56.000
Sample Bank organisation Gene expression filing PCR-card filing in MDS	MDS steering committee	10,000 10,000 10,000
		Annual support
Travel costs meetings		10.000
LeukemiaNet		47.964
Celgene		50.000
Pharma Consortium		53.666 ?

The budget assignments should be more specified. This will be discussed in Heidelberg. Please, send your comments per email.

Deliverables 2004/2005 (T. de Witte)

Actual state of deliverables are presented.
We have to report deliverables 2004 and 2005 to the NMC. The secretariat will mail a proposal for deliverables 2005 to participants. Please, send your comments per email to the secretariat.
Hellström proposes to form small groups in Heidelberg working out different issues.

Conclusion (T. de Witte)

-MDS WP has started to function.
-All major European MDS groups and experts participate actively. Please let us know when there are groups missing in MDS WP.
-Cooperation with MDS foundation: avoiding double reporting of studies should be an issue.
-Interaction with translational/diagnostic research groups should get priority.
-First contacts with pharmaceutical companies have been established recently.

Agenda next meetings will be adjusted to which participants will be present.

Action Items

Action	Coordinator	Target Date	Priority
Start with presentation of documents on the website of LeukemiaNet	De Witte		1
Trials: List all protocols of trials by MDS study groups in Europe on the website of LeukemiaNet	De Witte/Hellström		1
Trials: Presentation on the website of a format for study protocols	De Witte		1
Trials: New drug evaluation, trial availability	Fenaux		
Trials: Coordination of subgroups of ongoing and new clinical trials: Proposal for definition of responsibilities of coordinators	De Witte		
Trials: Subgroup Anticytokine and signal transduction modulating studies: Starting European 5q-Revlimid study	De Witte		
European **MDS registry**: List features existing databases and work out details of IT structure which can integrate these population based databases.	Bowen/ Bernasconi		1
European **MDS registry**: Define minimal datasets for registry	Bowen/ Bernasconi		1
European **MDS registry**: Subcommittee for the registry of MDS trial data works out detailed program	Hellström		1
First proposal on **guidelines** for diagnostic standards	Hellström		1
First proposal on **guidelines** for therapeutic approaches	Cazzola/Bowen		1
Sample banking: Find out which WP/ persons within LeukemiaNet are involved with this item. Proposal for translational research targets and information structure on who has stored what, with which data.	Jansen		1
Gene expression profiling: proposal for MDS	Hofmann		2
Interaction with AML WP regarding: Trials that target both MDS and AML patients Treatment decision-making for older patients with MDS or AML	Lübbert		
Interaction with MRD WP12	Padua/ Jansen		2
Interaction with CMPD WP	Germing		2