

Present

de Witte, Hellström-Lindberg, Ganser, Bowen, Lübbert, Jansen, Huber, Padua, Germing, Sanz, Hehlmann, Döhner, Amadori, Krejci, O'Neill, Lowenberg, Lo-Coco, Hasford, Mittelman, Hills, Wheatley, van de Loosdrecht, Büchner, Malcovati, Della Porta, Ossenkoppele, Cermak.

Next meetings

-Joint MDS/AML session „Novel targets, novel drugs“ during the Int. conference on differentiation therapy, Versailles France, 6 November 2006, 14h00-18h00, (R. Padua).
- 4th Annual Symposium of the ELN/8th Annual Meeting of the German Competence Network , 30 January to 1 February 2007, Heidelberg.

1. BCSH Guidelines for AML (see bcshguidelines.com) Deliverable 8.26

Integration of diagnostic guidelines in AML and MDS
Dr G Jackson could not be present and apologizes.

2. APL (Acute Promyelocytic Leukemia) guidelines and minimum dataset

Prof M Sanz

Objectives database

- To create and implement a networked database to share data between users at multiple sites and between cooperative groups.
- Features of the database (web-based tool) and plan for data-analysis were discussed.

-Definition of relapse risk and role of nonanthracycline drugs for consolidation in patients with acute promyelocytic leukemia: a joint study of the PETHEMA and GIMEMA cooperative groups.

-TREATMENT OF NEWLY DIAGNOSED ACUTE PROMYELOCYTIC LEUKEMIA (APL) : A COMPARISON BETWEEN FRENCH -BELGIAN-SWISS (APL group) AND SPANISH APPROACHES, For the European APL group and Spanish PETHEMA group, ASH meeting, Atlanta, GO 2005.

-We performed a joint analysis of Spanish PETHEMA and APL 2000 studies to compare their results in different risk categories.

APL Guidelines

- We are currently drafting a first version to be discussed in autumn with European experts in APL.
- Several recent documents will help us to draft the document: 1)BCSH Guidelines for AML; 2) NCI sponsored guidelines (Cheson et al., JCO 2003); “Tricks of the trade” paper (Sanz et al., Blood 2005).
- Final APL Guidelines: December

European Project for Salvage Therapy was presented.

3. Pick a winner design, AML in the elderly: new ideas for designing trials

Deliverable 8.35

Dr R Hills, Cardiff University, Cardiff UK

MRC trials - 3000 patients over 60 (and 6000 randomisations) since 1990. But no real improvement in survival!

Can we identify worthwhile drugs using fewer patients?

-We want to identify or rule out relatively large benefits.

-Good treatments should then show some evidence of benefit early on in the trial.

-AML 14 showed a benefit for Ara-C over hydroxyurea.

To improve OS need to improve CR rates (CR is short term outcome).

-AML16: Pick a winner/Dump a loser:

-Compare all candidate treatments with Ara-C.

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www.leukemia-net.org

T. de Witte, O.Huber, WP8

- After 50, 100 patients per arm look for evidence the treatment improves CR.
- If not, then drop that treatment.
- Include new treatments as they become available (6 or more different treatment arms, flexible design).

- Choose cut-offs dependent on the size of benefit that is worthwhile for this treatment (cost/toxicity/etc).
- Typically might want to increase CR rate from 15% to 30%.
- Only 7% of worthless treatments proceed to a full trial.

4. Prognostic index in the elderly Deliverable 8.24, 8.34

Prof K Wheatley, on behalf of the UK NCRI Haematological Oncology Clinical Studies Group

Prognostic factors in older AML patients receiving intensive and non-intensive therapy: Analysis of the UK AML11 and AML14 trials.

- Most prognostic/predictive factor work done in younger patients (<60 years).
- Fewer data on older patients, especially those receiving non-intensive therapy.

Trial Designs

- AML11: Conventional induction and consolidation therapy similar to that for younger patients, e.g. DAT 3+10, DAT 2+5, DAT 2+7.
- AML14I: Similar to AML11, e.g. DAT 3+10, DAT 3+8, MidAC.
- AML14NI: Non-Intensive therapy with hydroxyurea or low dose Ara-C (20mg b.d. for 10 days).

Endpoint and Methods

Overall survival analysed (similar work can be done for CR, DFS).
Univariate analysis of AML11 to identify important prognostic parameters.
Multivariate analysis (Cox regression), from which regression equation obtained.
Risk groups categorized.
Risk groups applied to AML14I and AML14NI – validation.
Risk groups created for AML14I and AML14NI data.

Summary

Possible to identify prognostic factors and risk groups in the elderly.
Similar parameters to younger patients.
Risk groups apply to both intensive and non-intensive therapy.
Can these risk groups be used to determine therapy, i.e. to decide which patients will benefit from intensive therapy and which will not?
Role of cytogenetics in treatment decision-making was discussed.

The Future

These analyses cannot determine optimal therapy for patients in different risk groups.
The only way to do this reliably is through randomised trials of intensive versus non-intensive therapy, stratified by risk group.
Clinician and patient preferences make these difficult studies to perform – AML14 intensive v. non-intensive randomisation: n=8.
But without them we will not get the answers!

Non-randomised Comparison

Intensive v. non-intensive arm entered into Cox regression.
Arm was most important variable (chi-squared values given).

5. Development of a common prognostic score for MDS and AML treated with intensive therapy Deliverable 8.34

Prof. De Witte

Prognostic factors

- Patient-related: Age, performance status, comorbidity, genetic variations in drug metabolism.
- Disease-related: Cytogenetic abnormalities, molecular aberrations.

Purpose of this analysis

To identify clinical and biologic prognostic factors for MDS and AML in intensively treated patients aged < 56 years.

Results

- CRIANT study N=203 (EORTC 06961).
- AML-10 study N=575 (EORTC 06931).
- Multivariate analysis for DFS (overall group N=516).
- However, some variables were of prognostic importance in only one of the studies.
- Therefore, a separate multivariate analysis of survival for both studies was made.

Conclusions

- Some prognostic factors are different in MDS and AML.
- Poor prognostic factors occur more often in MDS.
- The EORTC score is a valuable alternative for the IPSS in intensively treated patients.

Future perspectives

- Risk stratification based on prognostic model allows joint studies for AML and MDS.
- Incorporate molecular data in model (FLT-3)?
- Poor risk patients in investigational protocols.
- The EORTC score needs to be validated in other studies.

6. Immunophenotyping guidelines in MDS Deliverable 8.25 and new Deliverable?

Dr. van de Loosdrecht

A preliminary report on behalf of the MDS working party of the Dutch Society of Cytometry [NvC].

In AML, CLL, NHL, MM routine diagnostic procedure.
MDS complex and heterogeneous stem cell disorder.

Immunophenotype of myeloid blasts in MDS and survival in different IPSS subgroups was presented.

Diagnostic utility of IF in MDS:

- IF detects many abnormalities in granulocytic and monocytic maturation.
- IF identifies MDS where classical criteria fails.
- IF is more sensitive than morphology in assessing granulocytic dysplasia.
- Myeloid and monocytic dyspoiesis by IF scoring system correlates with IPSS and outcome after allo SCT.

Conclusions

- IF identifies aberrancies in granulocytic and monocytic lineages in MDS.
- IF classifies patients with [multi]-lineage aberrancies in MDS not otherwise determined by cytology [WHO].
- upgrading of MDS (?)
- IF supports basic concept of WHO: [pure] RA vs RCMD (+/- RS).

Future perspectives:

- First international WP[3] flow-cytometry in MDS on standards and standardization in MDS; Vienna July 2006
- review all current data

- identify Ags and standardize Abs/methods
- identify relevant control [normal] BM
- initiate a multicenter IF study in MDS
- Identifying Cytopenia with unknown significance as MDS.
- Insights into pathogenesis of MDS.
- Design of IF scoring system.
- Correlation with cytogenetics, IPSS, clinical parameters, disease progression.
- Characterization of progenitor cell/leukemic stem cell [LAP - MRD-technology].
- Evaluation of new additional LAPs (CLL-1).
- Characterization / quantification of dendritic cells and basophils in MDS.
- Implementation of IF as marker for disease monitoring in clinical trials with new drugs (Epo; G-CSF; anti-TNF; anti-VEGF; lenalidomide; decitabine).

7. Update on the progress of the development of guidelines for therapeutic procedures in MDS Deliverables 8.27, 8.28, 8.29

L. Malcovati

Next steps:

- evaluation of statements on key questions from the expert panel and definition of simulated clinical cases for scenario analysis;
- rating of scenarios by the expert panel and appropriateness analysis;
- possible final consensus conference and formulation of recommendations.

Proposal to ask several MDS groups from outside of Europe to comment on the guidelines.

See http://www.leukemia-net.org/content/e58/e525/e539/index_eng.html

8 Update on genetic analysis and apoptosis/cell cycle regulatory gene expression in MDS Deliverables 8.43, 8.44, 8.46

Dr. Jansen

I: Elucidating genetic aberrations in MDS (BAC arrays and SNP arrays)

42.000 overlapping clones Array-CGH: detection of chromosome 12 microdeletions in a t(12;22)(p13;q11-12) translocation => Deletion of part of the ETV6/tel gene.

Single nucleotide polymorphism arrays (SNP-array) identifies regions of homozygosity (due to deletions OR gene conversion).

=> We have chosen to change the platform and use 250.000 SNP arrays.

Current Status:

the first 46 MDS patients have been hybridized to the 250 k SNP-arrays.

Results awaits the bioinformatical analysis.

Goal:

Analyze a large panel (several hundreds) of MDS patients.

Patient selection: well defined, both cytogenetically, morphologically and clinically.

Additional material must be available for identification of the affected genes in the identified loci.

II: Expression pattern of apoptosis and cell cycle-related genes in FACS-sorted bone marrow subfractions in MDS

Expression of erythroid differentiation markers is increased in sorted CD71+ cells compared to sorted CD34+ cells.

Erythroid differentiation markers are comparable in MDS and normal sorted CD71+ bm-cells.

CARD-PCR: sustained overexpression of WT-1 in CD71+ MDS cells.

Microfluidic Card-Quantitative PCR, results sofar:

CARD has been designed, system has been tested.

CD34, CD71 and CD33/CD13 sub-fractions have been isolated by FACS-sorting.

CD34 and CD71 subfractions of 25 MDS patients (various subtypes) and normal controls have been analysed on CARD, ongoing.

Several genes show a MDS-specific gene expression pattern: some are CD34 specific, others CD71, some both.

=> Confirm in larger panel, test the CD33/CD13 fraction.

=> Add more patients of all subtypes.

III: Development of software for Integrated PCR & micro-array analysis

-Automated conversion of PCR data for integrated analysis of CARD, SNP/BAC array and patient data.

-For analysis of the PCR-expression data we developed an interface to enable the use the available software programs designed for analysis of micro-array expression data.

If interested to contribute samples: contact: j.jansen@chl.umcn.nl

9. Proposal for a protocol: Lenalidomide in high-risk myeloid disease with del(5q) Deliverable 8.7 or new deliverable?

Prof. Hellström

Coordination by Nordic MDS Group. Celgene is willing to support this study via a CRO.

See http://www.leukemia-net.org/content/e58/e525/e2248/index_eng.html

If interested to join, please contact: eva.hellstrom-lindberg@ki.se

10. Common standard arm update Deliverable 8.35

Prof Büchner

Proposal: joint arm for European AML/MDS studies: which schedule is preferred for the control arm?

Dr. Thomas Büchner proposed a European AML/MDS cooperation on the basis of cross-trial networking. This network combines various multicenter trials by two instruments, (1) a common standard treatment arm, and (2) a general up-front randomization by which 10% of the patients in each trial are assigned to the common standard arm.

The European AML/MDS network provides a validation of a trial strategy by comparison with the common standard arm and consequentially also with other trial strategies.

The contribution by each trial group is 10% of patients treated and documented according to the common standard arm whereas the specific tradition, strategy, philosophy, and autonomy of the group are maintained.

The German AML Intergroup may serve as a certain pilot project. Between Feb. 02 and Nov. 05 2140 patients younger than 60 years were recruited by the four participating trial groups with 219 patients assigned to the common standard arm. By recent updates OS and RFS in the four trial groups can be compared with those in the common standard arm. In the meantime, the attribution of the various Kaplan Meier plots remains blinded for the Intergroup.

Patients under age 60 currently receive for induction two courses of 7+3 (AraC 100 mg/m²/d X 7 + DNR 60 mg/m²/d X 3) (double induction). Post-remission therapy contains three courses of AraC 3 g/m² q 12 h X 6. A proposal for patients of 60+ years is under elaboration. So far, we suggest for induction 1-2 courses of 7+3 (AraC/DNR as above) with the second course only given to patients with 5% or more residual b. m. blasts (no double induction). The suggested post-remission therapy contains two courses of AraC 1 g/m² q 12 h X 6.

The proposal of a European AML/MDS cross-trial network is presently discussed among a number of national and paneuropean trial groups.