Haematological malignancies proffered papers discussion abstracts 2850 and 2860

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Disclosure slide

Roche
Cellgene
Mundipharma
Janssen

Gilead
Bayer
Millenium
Servier
High-dose vs. low-dose Ara-C in AML is a recurrent question

n = 725  Double induction without (TAD/TAD) or with HD AraC (18 g/m2)

OS

All patients

High-risk patients

Büchner et al, Blood 1999
Consolidation after HD Ara-C induction

n = 202, ICE induction, consolidation with either ICE (AraC 24 g/m2) or IcE (0.5 g/m2)

OS all patients

PFS by risk

Bradstock et al, Blood 2005
HD Ara-C to intensify conditioning

Japanese allo-transplant registry

CY-TBI 1’667
HD AC/Cy-TBI 435

Arai et al, J. Hematol. Oncol. 2015
Consolidation with HD Ara-C (3 g/m$^2$)
or iD Ara-C (1 g/m$^2$) + Anthracycline

Korean registry
HD Ara-C 58
iD Ara-C/Anthra 87

Kim et al, Ann Hematol 2015
The present study

• Population: children and adults
• Sample size: 170 recruited, 90 analyzed, 79 completed treatment
• Toxicity: comparable
• Design: standard induction (7+3), consolidation HD vs. iD Ara-C (both doses are high!)
• Relapse rate: high in both arms (55% vs. 51%)
• OS: significantly better for 18 g/m²
How to interpret the present study

• Response rate and response duration similar

• Survival different

• Too early, interim analysis only

• No sufficient power as yet to draw any conclusion
Myelodysplastic Syndromes (MDS)

- Heterogeneous disorders of hemopoietic stem cells
- Causes ineffective hemopoiesis
- Increased risk of transformation to AML
Pathogenesis of MDS

MDS are associated with:

• Genetic alterations (→ epigenetic)
• Repression of apoptosis
• Deregulation of the microenvironment
Epigenetics

«Changes in gene expression that are not due to alterations in DNA sequence”

Holliday, Science, 1987

• DNA methylation
• Histone modification
• RNA interference (mostly due to micro-RNA)
DNA methylation / demethylation

TET = Ten-Eleven-Translocation proteins
Demethylate cytosine

Ko et al, Immunol. reviews 2015
Epigenetic modifications in hematological malignancies

The mutation of some genes causes methylation or hypomethylation of potentially leukemogenic genes or change of the histone function.

DNA methyltransferase inhibitors and MDS

Azacitidine, Decitabine

Inhibit methyltransferase

Cytosine not methylated (DNA hypomethylation)

MDS reversed

RR in MDS: 20-40%
Prognostic factors for response

93 patients with MDS treated with azacitidine

Mutations detected  SF3B1  59/86
                   TET2  29/87
                   DNMT3A  12/87
                   ASXL1  5/89
                   JAK2  3/87

None predicted response to azacitidine

Thepot et al, ASH 2013
The present study

- 70 newly diagnosed MDS treated with 5 days decitabine
- RR 52.5% responders survive longer
- 17% mutation in methylating machinery genes
- RR mutated 83% non mutated 43%
How to interpret the present study

• Demethylating agents confirm to have a (modest) activity in MDS

• This activity is (possibly) higher in the presence of mutations in genes involved with the epigenetic machinery

• The predictive role of these gene mutations must be confirmed by further studies