Are we ready to use mutations and gene expression changes in treating AML?

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January 11, 2008
AML: Disease Paradigm

- Resistance to growth inhibition
- Evasion of apoptosis
- Immortalization
- Independence from mitogenic stimulation
- (Angiogenesis)
- Metastasis and invasion

Hahn and Weinberg, Rules for Making Human Tumor Cells. NEJM 2002;347:1593.
AML: Disease Paradigm

Class I:
- Proliferation, Survival advantage
- Flt3-ITD
- Flt3-TKD (?)
- N-Ras, K-Ras mutations

Class II:
- Impair differentiation, Impair apoptosis
- CBFβ/MYH11
- AML1/ETO
- PML/RARα
- MLL fusions
Cytogenetics

- At diagnosis, standard CG are normal in 40% of adults and 25% of children
- Intermediate prognosis (CR rate, RR, OS)
- OS 24-42% at 5 years
- CALGB improved RR and DFS by post-CR consolidation with
  - 4 cycles of HDAC or IDAC or
  - 1 cycle of HDAC/etoposide f/b autologous SCT
Ensure the Karyotype is Normal

- CG abnormal clones may only be detected in cells cultured x 24-48 hours
- PB CG are normal while the BM shows an abnormality in 5% of patients
- Cryptic insertions may cause the same fusion proteins as recurrent translocations or inversions
  - Detectable by FISH or RT-PCR
  - Routine only if morphology shows M3, M3v or M4Eo
- Spectral karyotyping, FISH with comprehensive genomic DNA probes, and cGH suggest most patients with CGN do **not** harbor unrecognized aberrations
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Heterogeneity of CG Normal AML

- Molecular markers assist with prognosis


Kottaridis et al. Blood 2001:1752 (MRC)
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Döhner et. al. Blood 2005;3740 (AMLSG)
Can CG and molecular markers aid in the choice of therapy?
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Figure 5. Donor versus no-donor analysis on relapse-free survival according the combined *NPM1* and *FLT3* ITD mutation status. (A) *NPM1*-mutated/*FLT3* ITD–negative patients. (B) All other patients.

Döhner et. al. Blood 2005;3740 (AMLSG), updated at ASH 2006
Can CG and molecular markers aid in the choice of therapy?

- **Flt3 ITD**
  - Flt 3 inhibitors (14 in devel.)

- **KIT N822 (exon 17), exon 8 mutations**
  - TKIs (imatinib, dasatinib)

- **KIT D618 (exon 17)**
  - PKC412 (staurosporine)

- **Ras** (mutation is not a prerequisite for response)
  - Farnesyl transferase inhibitors (tipifarnib)

- **CBF leukemias**
  - GO, demethylating agents

- **LSCs with ↑NFkB**
  - Parnetholides, IκB kinase inhibitors
Can CG and molecular markers aid in the choice of therapy?

- NPM+/Flt3 ITD- ATRA

The Genotype NPM1mut/FLT3-ITDneg Is a Highly Significant Predictive Factor for Response to Therapy with All-Trans Retinoic Acid in Acute Myeloid Leukemia – Results from AMLSG Trial AML HD98B.

Oral Session

Richard F. Schlenk, Konstanze Döhner, Michael Kneba, Francesco del Valle, Frank Hartmann, Heinz Kirchen, Elisabeth Koller, Katharina Götze, Jörg Th. Fischer, Marianne Habdank, Daniela Späth, Silja Groner, Andrea Corbacioglu, Axel Benner, Stefan Fröhling, Hartmut Döhner. Internal Medicine III, University of Ulm, Ulm, Germany; German-Austrian Acute Myeloid Leukemia Study Group (AMLSG), Germany
Rationale for ATRA in non-M3 AML

- Decreases bcl-2
- Increases histone acetylation
- Synergistic with cytarabine, idarubicin if given in the proper sequence
Prior Studies

- No impact on survival in various populations (7 prior studies)
- Exception: HD98B (Leukemia 2004)
- Importance of sequence
HD98B Design and Execution

14 + 242 patients ≥61 yo randomized 1998-2004

ICE-1 (n=120)

ICE-2 (n=52)
Rec’d allocated Rx n=44

HAM (n=46)
Rec’d allocated Rx n=36

No CR → A-HAE
(ICE 48, A-ICE 38)
Rec’d allocated Rx = 38

A-ICE-1 (n=122)
Rec’d allocated Rx n=119

A-ICE-2 (n=73)
Rec’d allocated Rx n=66

A-HAM (n=63)
Rec’d allocated Rx n=50

2nd Randomization (n=72)
IE PO vs. IE IV
HD98B Design and Execution

+ 116 patients

14 + 242 patients ≥61 yo randomized 1998-2004

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Demographics

- Median age 67 years
- Follow-up 6 years
- WBC 6.7
- De novo 2/3, secondary to MDS 1/3
Molecular Profiles

- Normal karyotype
- CBF
- Other

- NPM mut
- FLT3-ITD
- FLT3-TKD
- MLL-PTD
- CEPBA mut
Results

- ATRA did not significantly improve CR or OS
- But there was a significant interaction between ATRA and NPM+/Flt3 ITD-
  - Only 16 pts had this genotype in ATRA arm
  - Only 14 pts had this genotype in non-ATRA arm
- 5 yr OS this genotype + ATRA 57% (95% CI, 28-78%)
- 5 yr OS this genotype – ATRA 6% (95% CI, 0-25%)
Results

- Induction success:
  - CGN: OR 4.1
  - NPM1 mut/FLT3-ITD neg: OR 3.25
- ATRA was not significant for the overall population
- But for those with NPM1 mut/FLT3-ITD neg, ATRA did confer a marked benefit
Conclusions and Future Directions

- Genotype NPM mut/Flt3 ITD- predicts response to ATRA in an elderly cohort with non-M3 AML
- AMLSG plans a prospective study
  - 920 patients with NPM mutation
  - +/- FLT3-ITD
My Opinion

- Far worse OS with NPM+/Flt 3 ITD- in non-ATRA group than in previous trials – This is not addressed!
- Will this pan out in Phase III trial?
  - CIs approach each other; absolute difference may be fluke of the small sample size
  - No correction for multiple testing; data mining
- Primitive way to think about AML
- Need to integrate more information than a few molecular markers
- Would like a mechanistic explanation for why NPM+/Flt3 ITD- may respond to ATRA while other AMLs may not
Bottom Line

- We are starting to dissect apart AML
- Eventually we might choose therapy more rationally… but not yet