Acute Leukemia: new agents

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Therapeutic advances in Hematology
Societat Catalana d’Hematologia
Outcome of AML in adult patients: a real need for new agents

- Curation of only a fraction of patients (<50%) – insufficient antileukemic potential
- Remission is based on highly myelotoxic agents – toxicity
- Limited target population of hematopoietic stem-cell transplant
- “High-risk” presentation forms – need of a different/“more gentle APL-like approach”
Outcome for patients with AML: any improvement for the last two decades?

Acute Myeloid Leukemia (AML): temptative definition

- Genetically heterogeneous clonal disorder
- Origin in hematopoietic progenitor cells
- Due to accumulation of somatic acquired genetic & epigenetic alterations
- Altered mechanisms of self-renewal, proliferation & differentiation
- Resulting in an impaired *leukemic* hematopoietic hierarchy: the leukemia stem-cell model
Novel therapeutic strategies introduced in AML in recent years

• Intensified anthracyclines in induction therapy
• Addition of GO to CT (gemtuzumab ozogamycin, antiCD33+calicheamicin)
• Targeted therapy: TKIs (FLT3 inhibitors,...)
• Demethylating agents in AML
• Histone deacetylase inhibitors
• Priming with G-CSF: chemosensitizing or blocking stromal protection (CXCR4 antagonists)
• ...
High-dose daunorubicin in AML: benefit for good & intermediate-risk cytogenetics

Fernández HF (ECOG), NEJM 2009
MoAbs in AML: Humanized antiCD33 Ab Gemtuzumab + calicheamicin (Mylotarg)

1-2. Binding to CD33 Ag
3-4. Internalization & calicheamicin activation
8. Antitumoral effect: induction of DNA breaks
7. Mechanisms of resistance: drug efflux
5. Rapid CD33 re-expression
Mylotarg in relapsed AML: the old concept

✓ Significant activity but transient duration of response - monotherapy (9 mg/m² x 2 doses) for relapsed AML
  • 26% CR
  • Median response duration: 7 mos

✓ Significant hepatotoxicity (SOS)

✓ Uncertain synergy with chemotherapy

✓ Role in APL: chemo-free front-line, molecular relapses

Sievers E, JCO 2001
Larson R, Cancer 2005
Estey E, Blood 2002
Lo Coco F, Blood 2004
Mylotarg revisited: from early withdrawal to resurrection – a dose issue?

✓ Addition of a 6 mg/m² at day +4 of DA induction – excess of induction death in the GO arm (5.4 vs. <2%) - (SWOG S0106)

✓ Addition of low-dose GO (3 mg/m²) to induction & course 3: survival benefit in pts with favorable cytogenetics - MRC AML15 Trial

✓ Addition of multiple doses of GO (3 mg/m²) to standard AML chemotherapy: days 1, 4 & 7 during induction, day 1 of consolidation (x 2 courses) – ALFA-0701

Petersdorf S, ASH 2009
Burnett A, JCO 2011
Castaigne S, Lancet 2012
Mylotarg revisited (II): from early withdrawal to resurrection – a dose issue?

✓ Improved EFS, but not OS, in IR-AML pts receiving GO at a dose of 6 mg/m² at induction & consolidation who did not undergo alloHSCT– (GOELAMS AML 2006 IR Study)

✓ Toxicity related to GO:
  - Delayed plated recovery
  - Increased hepatic toxicity (6 mg/m²)

Delaunay J, ASH 2011
Castaigne S, Lancet 2012
Mylotarg revisited: benefit in frontline therapy

**EFS**

**OS**

Relapse-free survival

2-yr RFS: 50 (+GO) vs. 22.7%

De novo AML
50-70 year-old
280 randomized pts.

Castaigne S, Lancet 2012
Good-risk patients benefit from the addition of Mylotarg: MRC AML15 Trial

Burnett A, JCO 2011
FLT3 (fms-like TK) Internal Tandem Duplication (ITD)

Downstream FLT3 signaling

Alteration of transcription and translation: Regulators of cell cycle, apoptosis, differentiation

PROLIFERATION

SURVIVAL

DEGRADATION

BAD

AKT

PTEN

PI3-KINASE

MEKK

ERK

STATS

PM

Internal duplications

Point mutations

Insertions

Deletions
FLT3 inhibitors: diverse specificity against multiple targets
FLT3 inhibitors: currently existing experience

- Limited activity in **monotherapy** (sorafenib, midostaurin,…)
- Possible synergy in **combination with chemotherapy**
  - Lestaurtinib: no benefit in relapsed AML
  - Midostaurin/PKC-412: on-going trial (front-line tx)
- Role in the alloHSCT setting: anecdotal reports of responding patients
- AC220 (quizartinib): remarkable activity in monotherapy
  - Composite response rate (CR+CRp+CRi) of ≈45%
  - Differentiating potential in AML blasts

Fischer T, JCO 2010
Levis M, Blood 2011
Cortes J, Haematologica 2011
Lestaurntinib added to CT failed to improved outcome in relapsed AML

Control arm: CT (MEC or HiDAC)
Experimental arm: CT + lestaurntinib

Levis M et al. Blood 2011
Midostaurin (PKC412): experience combined to CT

- Sequential (day 8→21) or simultaneous (1→21) administration with CT (daunorubicin/SD ara-C)
- Reduced dose (50 mg BID) was better tolerated
- Results in 40 pts:
  - CR in 12/13 (92%) FLT3mut AML
  - CR in 20/26 (77%) FLT3wt
- Sequential regimen were better tolerated

Stone R, Blood 2005
RATIFY trial: exploring the effect of adding midostaurin (PKC412) to frontline CT in FLT3-ITD AML
AC220 as a bridge strategy to alloHSCT in a patient with a primary chemorefractory FLT3-ITD(+) patient

**Nov-2010**
50-yr male
WBC 81x10^9/L
AML w/o maturation +8, FLT3-ITD(+)

**May-2011**
- Pancreatitis
- BM fibrosis & 57% blast
- High FLT3-ITD/wt ratio
- 2 available HLA-id sibl

**IDA-FLAGx2-Ref**

**August-2011**
AlloHSCT
MAC (Cy/TBI)
HLA-id sibl

**AC220 x 2**

**May-2012**
+9 mos post-allo
cGvHD after CsA removal
CCR+
100% chimerism

**Response to AC220?**
Pancytopenia
Hypocellular BM
Absence of blasts – blast-free status
Persistent fibrosis
FLT3 inhibitors: an adequate target?

✓ FLT3-ITD: a frequent mutation (≈20%) & frequent FLT3 overexpression in unmutated FLT3 AML cases

✓ Driver or passenger mutation?

**Passenger mutation**
- Evolutive mutation
- Insufficient to induce AML in preclinical models
- Not present in all paired relapsed samples
- Highly variable allelic burden

**Driver mutation**
- Identification of TK domain mutations conferring resistance in relapsed patients
FLT3 mutations arising in relapsed pts under quizartinib involve critical residues for drug-target interaction – a mechanism of selected pressure

Mutations in 8/8 relapsed pts
Critical residues
“Polyclonal” resistance
Cross-resistance with sorafenib

FLT3-ITD as a driver mutation
FLT3-ITD involves LICs?
Confers oncogene addiction

Smith CC, Nature 2012
AML is a disease with deregulated epigenetic program: role for epigenetic therapy

DNA methylation (CpG islands) – demethylating agents
Histone deacetylation – HDAC inhibitors
Histone methylation
miRNA gene methylation
Epigenetic signatures in AML

Figueroa ME, Cancer Cell 2010
DNMT3A gene

• Encodes a 912 aa protein with DNA methyltransferase activity: catalyses CH3 addition to cytosine in CpG islands, leading to promoter silencing

• Multiple diverse DNMT3A gene mutations are found in AML

59.8% of the mutations are in R882
Demethylating agents in AML – possible development

• Monotherapy in pts unfit for intensive CT – benefit in “low-count” (20 – 30%) blast AML

• Role in higher blast %?

• Maintenance after CT-induced response – looking for a post-remission strategy in high-risk disease

• Combination with HDAC inhibitors – the García-Manero’s way

• In combination with frontline chemotherapy - Synergistic potential? Best time sequence? AMLSG 12-09 trial

• Aza after transplant – pre-emptive/therapy for relapse
Azacitidine Prolongs Survival (vs. Conventional Care Regimens) in Elderly Patients With Low Bone Marrow Blast Count AML

Fenaux P et al. JCO 2010
Demethylating agents in AML – possible development

- Benefit (prolonged response) for a subgroup of pts – tools for identifying predictors
- No eradicative potential – need to associate to other strategies
- Reasons for non-eradicative nature - evasion of LSCs?
- True mechanism of action of demethylating agents: more than CpG demethylation
- Optimal dose – regimen are still unknown
Survival according to age: Swedish Acute Leukemia Registry (1997-2005)

Overall survival according to age irrespective of management (top, n = 2767)

Increasing incidence of AML with age: a work of years

Acute myeloid leukemia (AML)

Males

Females

Rate per 1 000 000 person-years

Non-Hispanic whites
Blacks
Hispanic whites
Asians/Pacific Islanders

New agents for elderly AML patients – urgent progress needed!

- Absence of benefit with intensive CT – selected pts with highly chemosensitive AML

- How to be more efficient in the search of new agents? The “pick-a-winner” MRC approach
  - Multitesting several with “control arm”
  - Interim assessment to avoid useless recruitment
  - Response rate is a valid surrogate?
## Constant search of new agents for AML

<table>
<thead>
<tr>
<th>Evaluated</th>
<th>Under evaluation</th>
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<tbody>
<tr>
<td>MDR inhibitors</td>
<td>Newer nucleoside analogs (clofarabine, troxacytabine, elacytarabine,...)</td>
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<tr>
<td>Farnesyl-transferase inhibitors (tipifarnib,...)</td>
<td>FLT3 inhibitors</td>
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<tr>
<td>Lestaurntinib (FLT3 inh)</td>
<td>Demethylating agents</td>
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<tr>
<td>Laromustine (cloretazine)</td>
<td>Histone modifiers (HDACs)</td>
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<tr>
<td>Amonafide</td>
<td>Aminopeptidase inhibitors</td>
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<tr>
<td>Arsenic Trioxide</td>
<td>Hedgehog inhibitors</td>
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<tr>
<td>ATRA+CT in non-APL</td>
<td>NEDD8-Activating Enzyme (NAE) inhibitors</td>
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...
Clofarabine + LDAC: Outcome (N=70)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Clo N=16</th>
<th>Clo+ara-C N=54</th>
<th>Total N=70</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR + CRp</td>
<td>31%</td>
<td>67% (63%)</td>
<td>59% (56%)</td>
</tr>
<tr>
<td>Resistance</td>
<td>38%</td>
<td>20%</td>
<td>23%</td>
</tr>
<tr>
<td>Induction deaths</td>
<td>31%</td>
<td>19%</td>
<td>21%</td>
</tr>
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*p ≤ .05

Faderl S. Blood 2008;112:1638
Analyzing causes of failure - challenges for developing a curative therapy in AML

- Biological heterogeneity – not a unique target
- Multi-step process – lessons from whole-genome sequencing
- Quiescence of leukemia-stem cells confers chemoresistance – need to target LSCs
- AML: a family of different subclones – preleukemic & evolutive clones
- BM microenvironment – a protective *milieu*
Lessons from complete sequencing of AML

- Concurrence of multiple mutations per patient (>8):
  - A set of recurrent mutated genes (>50)
  - Most commonly mutated genes: *FLT3* (36%), *NPM1* (25%), *DNMT3A* (21%), *IDH1* (18%), *IDH2* (10%), *TET2* (10%), *ASXL1* (6%), *NRAS* (6%), *TTN* (6%) & *WT1* (6%)
  - Mutation in genes previously unknown
  - New leukemic pathways unraveled: the cohesin complex (*STAG2, SMC1A/3, RAD21*)
  - Subtype-specific mutations & other *transversal* mutations

John Welch/T Ley (University of Washington), ASH 2011
Origin of relapse in AML: evolution from founding clone / subclone / ancestral clone?
Why are LSCs important?

Conventional therapy

Anti-LSC therapy

Cortesía de Ruth M. Risueño
Potential mechanisms for targeting Leukemia Stem Cells

• Targeting fusion proteins
  - High diversity in AML

• Signaling pathways (JAK/STAT, Wnt, Hedghog,…)
  - Diversity
  - Redundancy-overlapping

• Self-renewal mechanisms
  - Similarity HSCs - LSCs

• Inducing differentiation – the ATRA model

• MoAbs against specific LSC Ags
AML biology: putative involved pathways
Selective targeting of Leukemia-Stem Cells: still an utopy?

Kikushige Y, Cell Stem Cell 2010
Self-renewal/Differentiation balance in HSCs/LSCs: promoting differentiation induces LSC apoptosis

Sachlos E, Risueño RM, Cell 2012
Chemical screening of compounds leading to loss of pluripotency (LOP)

Selection of selective compounds against LSCs

Differentiation / Self-renewal

Oct4 & Sox2 expression

Sachlos E, Risueño RM, Cell 2012
AML & hematopoietic niche: protection, disruption

Lane SW et al, Blood 2009
Mobilization of AML blasts after CXCR4 antagonist plerixafor: a true chemosensitization method?

Adult ALL – state-of the art

- Despite high initial response, less than 50% of pts are cured – insufficient antileukemic potential of current agents
- Dense-intense regimens used in adult B-ALL cause significant toxicity
- AlloHSCT arises as the only curative option for very high-risk subsets
- Need to identify future relapsers:
  - Sensitive assessment of MRD (the era of MRD-based protocols)
  - High-risk molecular markers (del IKAROS, MLL-r,...)
Blinatumomab: bispecific (CD19-CD3) recombinant antibody
Blinatumomab for eradication of MRD in B-ALL: experience in a Phase-II trial

- Adult B-ALL in morphological CR with detectable MRD at molecular level (≥1 x 10^{-4}) after induction/consolidation – molecularly refractory or molecular relapse
- Blinatumomab at 15µg/m^2 as continuous infusion x 4 weeks (1 – 4 cycles). AlloHSCT was proposed in responders
- 20 pts evaluable:
  - Obtention of molCR in 16 (80%) after 1st cycle
  - Active in molecularly refractory and high burden MRD

Topp MS (GMALL), JCO 2011
Sustained response after Blinatumomab in MRD(+) B-ALL

4/16 relapses
0/8 in pts undergoing alloHSCT

No Hematologic Relapse (probability)

Duration of Disease-Free Survival (days)

Topp MS (GMALL), JCO 2011
Blinatumomab: *unexpected* adverse events

- High frequency of serious CNS events (ataxia-apraxia, aphasia, seizures, cognitive disturbance,…) with first doses
- Cytokine release syndrome (CRS) with DIC in pts with high-burden disease
- Lowering initial dose & pre-phase with dexamethasone ±cyclophosphamide to prevent CRS
Blinatumomab: considerations & future development

- Role in overt-morphological refractory/relapsed B-ALL
- Role in other B-cell malignancies
- Mechanisms of disease *escape*:
  - Body sanctuaries (CNS, testis)
  - Loss of CD19 expression
- Future development of new targets for bispecific moAbs:
  - Anti CD33-CD3 (AML)
Role of NOTCH mutations in T-ALL pathogenesis: an opportunity for targeted therapy

Ligand-activated transcription factor

NOTCH activation requires 2 proteolytic steps

- Anabolic glycolysis
- Cell growth (PI3K-AKT-mTOR)

Ferrando A, ASH 2009
Aberrant NOTCH1 signaling in T-ALL

• Constitutive activation of NOTCH1 is found in \( \approx 60\% \) of T-ALL

• Gamma-secretase (GS) cleavage is essential for NOTCH1 activation:
  – GS inhibitors (GSIs) are a potential targeted therapy (GSI PF-03084014, MK-0752)
Benefits of combined GSIs + dexamethasone:
↓ less GI toxicity, ↑ anti-leukemic effect

Real PJ et al., Nature Medicine 2009
New agents for acute leukemia – remarks (I)

- Progress in AML/ALL biology knowledge is essential for developing new therapies
- Heterogeneity of disease – analysis of benefit in specific populations
- Multistep disease – need of combining agents against diverse targets
- Targeting LSCs: hope for cure
New agents for AL – remarks (II)

- Interfering with microenvironment protection might increase antileukemic efficacy
- Need to develop more rapid strategies for identifying active compounds
- Relevant role of clinical trials to improve outcome: company vs. non-benefit groups sponsored trials
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