Acute Leukemia Global Summit

Hot topics and latest advances in AML

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Reggio Calabria, Italy
Acute Myeloid Leukemia (AML)

- Clonal malignant disease of myeloid cells, a rare disease
  - It is more commonly diagnosed in developed countries
  - Annual incidence rate in Europe is about 3.62 per 100,000
  - 25% of all leukemias in adults
  - Primarily affects adults and children <1 year old
    - In general risk increases with age
    - Most common in people over 65 years old
Typically a disease of the elderly

Clinical Presentation

- Loss of appetite or weight loss
- Mild fever
- Symptoms and signs of altered function of blood cell cells
  - Red blood cells - anemia
    - Fatigue
    - Shortness of breath on exertion
  - Platelets – thrombocytopenia-
    - Easy bruising
    - Petechiae
    - Bleeding in the nose or from the gums
    - Prolonged bleeding from minor cuts
  - White blood cells (importantly neutrophils) – leukopenia/neutropenia
    - Recurrent minor infections or poor healing of minor cuts
    - Pneumonia

# AML: Predisposing Factors

<table>
<thead>
<tr>
<th>Antecedent Blood Disorder</th>
<th>Environmental Factors &amp; Lifestyle</th>
<th>Drugs</th>
<th>Genetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelodysplastic syndromes</td>
<td>Radiation exposure</td>
<td>Alkylating agents (cyclophosphamide, melphalan, nitrogen mustard)</td>
<td>Bloom syndrome</td>
</tr>
<tr>
<td>Chronic myeloid leukemia</td>
<td>Benzene</td>
<td>Topo-II inhibitors (etoposide, teniposide)</td>
<td>Fanconi anemia</td>
</tr>
<tr>
<td>Polycythemia vera</td>
<td>Smoking</td>
<td>Chloramphenical</td>
<td>Kostmann syndrome</td>
</tr>
<tr>
<td>Essential thrombocythemia</td>
<td>Alcohol use</td>
<td>Phenylbutazone</td>
<td>Wiskoff-Aldrich syndrome</td>
</tr>
<tr>
<td>Myelofibrosis</td>
<td>Dyes</td>
<td>Chloroquine</td>
<td>Ataxia-teleangiectasia</td>
</tr>
<tr>
<td>Paroxysmal nocturnal hemoglobinuria</td>
<td>Herbicides</td>
<td>Methoxypsoralen</td>
<td>Down syndrome</td>
</tr>
<tr>
<td>Aplastic anemia</td>
<td>Pesticides</td>
<td></td>
<td>Klinfelter syndrome</td>
</tr>
<tr>
<td></td>
<td>Obesity</td>
<td></td>
<td>Patau syndrome</td>
</tr>
</tbody>
</table>
Nomenclature

Major clinical and pathogenetic distinction

1) Primary or *de novo* AML

2) Secondary AML
   - Secondary to previous therapy (tAML)
   - Secondary to previous haematological disease

WHO Classification – importance of genetics

<table>
<thead>
<tr>
<th>Acute myeloid leukemia (AML) and related neoplasms</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML with recurrent genetic abnormalities</td>
</tr>
<tr>
<td>AML with t(8;21)(q22;q22.1);RUNX1-RUNX1T1</td>
</tr>
<tr>
<td>AML with inv(16)(p13.1;q22) or t(16;16)(p13.1;q22);CBFB-MYH11</td>
</tr>
<tr>
<td>APL with PML-RARA</td>
</tr>
<tr>
<td>AML with t(9;11)(p21.3;q23.3);MLLT3-KMT2A</td>
</tr>
<tr>
<td>AML with t(6;9)(p23;q34.1);DEK-NUP214</td>
</tr>
<tr>
<td>AML with inv(3)(q21.3;q26.2) or t(3;3)(q21.3;q26.2);GATA2, MECOM</td>
</tr>
<tr>
<td>AML (megakaryoblastic) with t(1;22)(p13.3;q13.3);RBM15-MKL1</td>
</tr>
<tr>
<td>Provisional entity: AML with BCR-ABL1</td>
</tr>
<tr>
<td>AML with mutated NPM1</td>
</tr>
<tr>
<td>AML with biallelic mutations of CEBPA</td>
</tr>
<tr>
<td>Provisional entity: AML with mutated RUNX1</td>
</tr>
<tr>
<td>AML with myelodysplasia-related changes</td>
</tr>
<tr>
<td>Therapy-related myeloid neoplasms</td>
</tr>
</tbody>
</table>

WHO Classification

**AML not otherwise specified (NOS)**
- AML with minimal differentiation
- AML without maturation
- AML with maturation
- Acute myelomonocytic leukaemia
- Acute monoblastic and monocytic leukaemia
- Acute erythroid leukaemia
- Acute megakaryoblastic leukaemia
- Acute basophilic leukaemia
- Acute panmyelosis with myelofibrosis

Myeloid sarcoma, Myeloid proliferations related to Down syndrome, Blastic plasmacytoid dendritic cell neoplasm

Prognostic Indicators

Age
- 5-year survival of AML patients <65 years about 40%
- 5-year survival of AML patients 65-74 years about 11%
- 5-year survival of AML patients >75 years about 1%

- De novo vs secondary AML
  - WBC at presentation
  - CNS disease

- Treatment response

- Cytogenetics
  - good prognosis: t(15;17), t(8;21), inv(16)
  - poor prognosis: -7, del(7q), -5, del(5q), 3q21/3q26 abnormality, complex karyotype

AML in the Elderly

Advanced age is a poor prognostic factor

- Reduced ability to tolerate chemotherapy or transplant
- Different disease biology
  - Frequent adverse cytogenetic profile
  - Frequent antecedent hematologic disorder

Bone Marrow Cytogenetics and the Elderly


2017 European LeukemiaNet prognostic genetic markers

**2017 ELN prognostic marker**

- FLT3
- CEBPA
- NPM1
- ASXL1
- RUNX1
- TP53

**Discovery**

- Additional 236 genes associated with myeloid neoplasms

- *Diagnostic samples from 475 patients who gave informed consent for biobanking (66% of randomized patients in a clinical trial)*

AML: diagnostic and prognostic work-up

Classical testing
- Peripheral blood count
- Peripheral blood morphology
- Bone marrow
  - Morphology
  - Multiparameter flow cytometry (Leukemia-associ. immunophenotype)
- Within 10 days
  - Cytogenetics

Genetic profile

Molecular screening
- PML-RARA
- RUNX1-RUNX1T1
- CBFB-MYH11
- MLLT3-KMT2A
- BCR-ABL1
- NPM1
- CEBPA
- FLT3
- IDH1/2
- RUNX1
- ASXL1
- TP53
- NGS gene panel

Within 24-48 hrs

Within 1st cycle
Mechanisms of illness of AML

AML causes morbidity and mortality through three general mechanisms:

1. Deficiency in normal blood cell number or function
   - Replacement of normal with malignant cells (crowding out)
   - Direct growth inhibition
2. Invasion of vital organs with impairment of organ function
3. Systemic disturbances by metabolic imbalance

Cytotoxic chemotherapy is also associated with significant morbidity

➢ Often difficult to distinguish between treatment effects and disease effects

Deficiency in normal blood cell number or function: consequences

- **Infection**
  Due to abnormal white blood cells (neutrophils)

- **Haemorrhage**
  Due to abnormal platelets
  Disseminated intravascular coagulation

- **Anaemia**
  Due to reduced red cell count
Traditional AML Treatment: Induction Chemotherapy (IC) for fit patients

• Rationale
  • Aimed at quickly getting rid of as many leukemia cells as possible
  • Intensity of treatment depends on patient’s age and health
  • Doctors often give the most intensive therapy to patients younger than 60 years, but some older fit patients may benefit from similar or slightly less intensive treatment

  ▪ In younger patients (eg, < 60 years), induction often involves treatment with 2 chemotherapy drugs
    - Still 7+3! (may change)
      - Since 1973
      - 7+3 = 7 days of cytarabine + 3 days of anthracycline

Induction Chemotherapy

- Aims to induce complete remission (CR)
  - Bone marrow blasts <5%
  - Improvements (near normalization) of blood counts

<table>
<thead>
<tr>
<th>Impact of Age on CR rate</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>&lt;35</td>
</tr>
<tr>
<td>CR rate (%)</td>
</tr>
</tbody>
</table>

Induction Chemotherapy

Predictors of poor response

- Poor performance status
- Age >60 years
- Unfavourable karyotype
- Antecedent hematological disease
- Multi-drug resistance phenotype
- Unfavourable gene mutations

AML Risk Categories: Response to Chemotherapy

Typically **good responders**:  
- Core-binding-factor leukemias (without c-KIT mutation)  
  - $\rightarrow$ t(8;21), t(16;16), inv(16)  
- Diploid AML with *NPM1* and *CEBPA* mutation (without *FLT3* mutation)

Generally **poor responders**:  
- Older patients  
- AML with adverse cytogenetics  
  - Complex karyotype, monosomal karyotype, *TP53* gene mutation  
- AML with *FLT3*-ITD  
- Secondary AML  
  - Treatment-related AML  
  - AML with myelodysplasia-related changes

Typical 7+3 AML Chemotherapy Hospital Course

- Administer chemotherapy
- Day 14 bone marrow analysis: goal is “empty”, i.e., <10% to 20% cellularity, residual blasts < 5% to 10%
- If blasts remain, re-induction is appropriate (usually 5+2)
- Await recovery (usually at least 21 days from start)
- Empty marrow ≠ remission!
- CR determined by morphology (microscope): cellular marrow < 5% blasts, independent of transfusions, neutrophils ≥ 1000/µL, platelets ≥ 100K/µL
- Determination of minimal residual disease (MRD) by laboratory assessment (flow cytometry or gene profiling) as it predicts relapse
Traditional Stages of AML Treatment: After remission

- **Consolidation**
  - Induction considered successful if remission is achieved
  - Further treatment (ie, consolidation) given to try to destroy any remaining leukemia cells and help prevent a relapse

- For younger patients (typically < 60 years), main options for consolidation therapy include:
  - Several cycles of chemo with high-dose cytarabine (ara-C; HiDAC)
  - Allogeneic (donor) stem cell transplant
    - The best option for each patient depends on the risk of the leukemia coming back after treatment, as well as other factors
Hypomethylating agents: remarks

Commercially available: Azacitidine and decitabine for AML patients who cannot receive intensive chemotherapy

How do they work?
slow the production of leukemia cells and help the bone marrow produce more healthy and normal functioning cells.

Goals of therapy:
to help increase blood cell counts
not commonly given with the goal of cure, but may help patients live longer.

➢ effective also in older patients with adverse cytogenetics. This is an important difference with conventional chemotherapy.

➢ meaningful clinical activity (eg, transfusion independency) and improved survival, even if complete remission is not achieved.

And for those who are not in complete remission (relapsed/refractory, R-R)? Recent drug approvals in AML

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target</th>
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</thead>
<tbody>
<tr>
<td>Midostaurin</td>
<td>FLT3 and de novo young AML</td>
</tr>
<tr>
<td>CPX-351</td>
<td>AML-MRC / tAML</td>
</tr>
<tr>
<td>Enasidenib</td>
<td>IDH2 and R-R AML</td>
</tr>
<tr>
<td>Gemtuzumab Ozogamicin</td>
<td>CD33 –frontline AML</td>
</tr>
<tr>
<td>Ivosidenib</td>
<td>IDH1 and R-R AML</td>
</tr>
<tr>
<td>Glasdegib</td>
<td>Sonic hedgehog frontline AML if IC not indicated in combo with ARA-C</td>
</tr>
<tr>
<td>Gilteritinib</td>
<td>FLT3 and R-R AML</td>
</tr>
<tr>
<td>Venetoclax</td>
<td>BCL2 frontline AML if IC not indicated in combo with hypomethylating agents or low dose ARA-C</td>
</tr>
</tbody>
</table>

MRC, myelodysplasia-related changes
R-R, relapsed/refractory
CPX-351

• Approved for the treatment of adults with newly diagnosed, therapy-related AML (tAML) or AML with myelodysplasia-related changes (MRC)

• CPX-351 is a liposomal formulation of cytarabine and daunorubicin encapsulated at a 5:1 molar ratio within 100-nm diameter liposomes¹
  – Drug exposure maintained >7 days after last dose¹
  – Evidence for selective uptake by leukemic vs normal cells in bone marrow of leukemia-bearing mice³

  – 1 unit: 1 mg cytarabine, 0.44 mg dauno¹

Promising AML Treatment
CC-486 (oral azacitidine) as Maintenance Therapy in First-Remission AML

International, multicenter, randomized, placebo-controlled, double-blind, phase III study

Fit patients ≥ 55 yrs with de novo or secondary AML in first complete remission (CR) with chemotherapy; intermediate or poor risk cytogenetics; ineligible for transplant; adequate bone marrow recovery (N = 472)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>300 mg QD x 14 days (28-day cycle)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC-486</td>
<td>n = 238</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Placebo</th>
<th>QD x 14 days (28-day cycle)*</th>
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<tbody>
<tr>
<td></td>
<td>n = 234</td>
</tr>
</tbody>
</table>

*Response assessment every 3 cycles. Patients with CR remained on treatment, patients with 5-15% BM blasts had option to increase treatment to 21 days/cycle, patients with > 15% bone marrow blasts stopped treatment.

Significant advantage on overall and relapse free survival (doubles survival time) with stability of quality of life

Wei. ASH 2019. Roboz, EHA 2020
Gilteritinib clinical development

The presence of FLT3-ITD mutations is associated with high rates of relapse and poor overall survival after standard intensive cytarabine (AraC)/anthracycline chemotherapy

Once daily oral tablet (40 mg)

Gilteritinib in combination with “7+3” induction and HiDAC consolidation in newly diagnosed AML (Phase 1)

• Safe in combination with intensive induction chemotherapy (n=66)
• Maximum tolerated dose with induction or consolidation: 3 tablets (120 mg/day)
  • (8%) discontinued treatment permanently due to an adverse reaction.
• Antileukemic activity in FLT3-mutated AML (n=33)
  ▶ Complete remission rate: 94%


Astellas clinical development

http://www.astellasamltrials.com (assessed on January 20, 2019)
IDH inhibitors + intensive chemotherapy in patients with newly diagnosed AML with \textit{IDH1} or \textit{IDH2} mutation

\textbf{Ivosidenib (n=60)}
- Median age: 62.5 yrs
- CRc: 80% (CR: 71%)

\textbf{Enasidenib (n=93)}
- Median age: 63 yrs
- CRc: 72% (CR: 56%)

Enasidenib Plus AZA vs AZA in Mutant IDH2 Newly Diagnosed AML—Phase II Randomized trial

Adult patients with mutant IDH2 ND AML, ineligible for intensive CT and no history of treatment with hypomethylating agents (N = 101)

Enasidenib 100 mg QD + Azacitidine 75 mg/m²/day SQ x 7 days/28-day cycle (n = 68)

Azacitidine Monotherapy 75 mg/m²/day SQ x 7 days/28-day cycle (n = 33)

Advantage on event-free survival

Ivosidenib + Azacitidine in Newly Diagnosed AML

23 pts; median age 76 yrs (61-88); age ≥ 75 yrs 52%
CR 61%; CRh 9%; CR + CRh 70%
12-mos OS 82%
IDH1 mutation clearance in 63% of CR-CRh

Azacitidine ± Venetoclax in Treatment-Naive Patients With AML Ineligible For Standard Induction Therapy

Multicenter, double-blind, placebo-controlled, randomized phase III trial

Adults with previously untreated AML ineligible for standard cytarabine/anthracycline due to age (≥ 75 yrs) or comorbidities, no hypomethylating agent for antecedent hematologic disorder (N = 431)

- Azacitidine 75 mg/m² SC or IV QD for D1-7 + Venetoclax 400 mg PO QD (with 3 day ramp up in cycle 1) on 28-day cycles (n = 286)
- Azacitidine 75 mg/m² SC or IV QD for D1-7 + Placebo PO QD on 28-day cycles (n = 145)

The combination prolongs survival.

### Response to AZA + VEN: Response and EFS

<table>
<thead>
<tr>
<th></th>
<th>Aza + Ven (n = 286)</th>
<th>Aza + Pbo (n = 145)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR rate (95% CI), %</td>
<td>66.4 (60.6-71.9)</td>
<td>28.3 (21.1-36.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CR by start of cycle 2 (95% CI), %</td>
<td>43.4 (37.5-49.3)</td>
<td>7.6 (3.8-13.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CR rate (95% CI), %</td>
<td>36.7 (31.1-42.6)</td>
<td>17.9 (12.1-25.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Transfusion independence* (95% CI), %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Red blood cells</td>
<td>59.8 (53.9-65.5)</td>
<td>35.2 (27.4-43.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>▪ Platelets</td>
<td>68.5 (62.8-73.9)</td>
<td>49.7 (41.3-58.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CR + CRi rate in subgroups (95% CI), %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ IDH1/2</td>
<td>75.4 (62.7-85.5)</td>
<td>10.7 (2.3-28.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>▪ FLT3</td>
<td>72.4 (52.8-87.3)</td>
<td>36.4 (17.2-59.3)</td>
<td>.021</td>
</tr>
<tr>
<td>▪ NPM1</td>
<td>66.7 (46.0-83.5)</td>
<td>23.5 (6.8-49.9)</td>
<td>.012</td>
</tr>
<tr>
<td>▪ TP53</td>
<td>55.3 (38.3-71.4)</td>
<td>0</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Combination AZA + VEN

- More remissions
- More transfusion independence
- Prolongs survival

AZA, azacitidine; CR, complete remission; PBO, placebo; VEN, venetoclax.
TP53 mutations: why are they “bad”? 

TP53 mutations are seen in 5-10% of de novo MDS/AML and increase to 25-40% in therapy related AML

TP53 mutations are seen in 50% of those with complex karyotype

Poor and/or very short response to treatment, including intensive chemotherapy, hypomethylating agents, and high risk of relapse post allogeneic SCT
## Targeting P53 Dysfunction in AML

<table>
<thead>
<tr>
<th>Mutations</th>
<th>Gene therapy</th>
<th>TP53 mutated</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gendicine/Advexin ONYX-015</td>
<td>TP53-SLP INGN-225</td>
</tr>
<tr>
<td>Vaccinating against p53</td>
<td></td>
<td>PRIMA-1/APR-246 MIRA-1/3 STIMA-1 CP-31398</td>
</tr>
<tr>
<td>Reactivation of mutant p53</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP53 wild-type</td>
<td>MDM2 (-p53 interaction) inhibitors</td>
<td>Nutlins/RG7112 MI compounds PXN727/822 JNJ-26854165 RITA</td>
</tr>
</tbody>
</table>

APR-246 Combined with AZA in TP53 Mutated AML
Best Response

<table>
<thead>
<tr>
<th>Evaluable patients*</th>
<th>AML20-30</th>
<th>AML&gt; 30</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=9</td>
<td>n=2</td>
</tr>
<tr>
<td>ORR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>78%</td>
<td>100%</td>
</tr>
<tr>
<td>CRi/mCR/MLFS</td>
<td>33%</td>
<td>0%</td>
</tr>
<tr>
<td>PR</td>
<td>22%</td>
<td>50%</td>
</tr>
<tr>
<td>SD with HI</td>
<td>11%</td>
<td>0%</td>
</tr>
</tbody>
</table>

* ie patients who received at least 3 cycles and had a marrow evaluation after 3 cycles

Cluzeau T, et al. EHA 2020 oral presentation
## APR-246 Combined with AZA: side effects

<table>
<thead>
<tr>
<th></th>
<th>All grade n=52</th>
<th>Grade 3/4* n=52</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Febrile neutropenia</strong></td>
<td>19 (37%)</td>
<td>19 (37%)</td>
</tr>
<tr>
<td><strong>Neurological</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ataxia</td>
<td>13 (25%)</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>4 (8%)</td>
<td>0</td>
</tr>
<tr>
<td>Acute confusion</td>
<td>4 (8%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Isolated dizziness</td>
<td>3 (6%)</td>
<td>0</td>
</tr>
<tr>
<td>Facial paresthesia</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Neurological toxicity manageable:**
- Full reversibility within 5 days of drug discontinuation
- No recurrence after dose reduction (one (13) or two (4) dose reduction)

**Neurological toxicity related to:**
- Lower glomerular filtration rate at treatment onset (p<0.01)
- Higher age (p=0.05)

Cluzeau T, et al. EHA 2020 oral presentation
Extracellular Targets for Investigational AML Therapies

<table>
<thead>
<tr>
<th>Agent</th>
<th>Modality</th>
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<tbody>
<tr>
<td>MBG453</td>
<td>Monoclonal Ab</td>
</tr>
<tr>
<td>AMV564</td>
<td>BITE</td>
</tr>
<tr>
<td>UCAR123</td>
<td>CAR-T</td>
</tr>
<tr>
<td>Magrolimab</td>
<td>Monoclonal Ab</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>Monoclonal Ab</td>
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</tbody>
</table>
Strong rationale for MBG453 blockade of TIM-3 in MDS/AML

• MBG453 is a high-affinity, humanized, IgG4 anti-TIM-3 monoclonal antibody that enhances immune cell-mediated killing of AML cells in vitro\(^1,2\)

• MBG453 simultaneously targets immune effector cells as well as leukemic stem cells and blasts\(^2\)
Trial design: Phase 1b study of MBG453 + HMA in MDS/AML

Up to 207 Adult Patients
- IPSS-R high- or very high-risk MDS (HR-MDS)
- Unfit, newly diagnosed AML, ineligible for standard chemotherapy
- R/R AML, ineligible for standard chemotherapy

Patients with prior HMA treatment for MDS/AML were excluded

ClinicalTrials.gov identifier: NCT03066648

8 countries 11 trial centers

Primary Endpoints:
- Maximum tolerated dose/recommended dose, safety and tolerability

Secondary Endpoints:
- Preliminary efficacy, pharmacokinetics

Additional study arms
- MBG453 ± spartalizumab (anti-PD-1)
- Spartalizumab + decitabine
- Spartalizumab + decitabine + MBG453

Decitabine Arm
- Days 1-5
- 20 mg/m²
- Started Aug 2017

Azacitidine Arm
- Days 1-7
- 75 mg/m²
- Started Feb 2019

28-day treatment cycles

MBG453 Day 8
- 240 mg Q2W
- 400 mg Q2W
- 800 mg Q4W

MBG453 Day 22
- 240 mg Q2W
- 400 mg Q2W

Borate U, et al. EHA oral presentation
MBG-453 and hypmethylating agents: Responses

ORR, overall response rate
R/R, Relapsed/refractory

ORR with MBG453 + decitabine in patients with R/R AML (26 evaluable\(^a\)) was 23% (all CRi)

Sallman D, et al. EHA oral presentation
MBG453 + HMA is safe and well tolerated in HR-MDS and AML

TEAEs occurring in ≥15% of patients overall

MBG453 + Decitabine (N=69)
Median exposure: 4.3 (0.7–30.3) months

MBG453 + Azacitidine (N=37)
Median exposure: 3.1 (0.3–12.3) months

- Most commonly reported TEAEs were consistent with those for HMA alone
- No maximum tolerated dose was reached
- No treatment-related deaths occurred
- Treatment discontinuation due to AE occurred in only 4 of 106 patients (2.3%)

Borate U, et al. EHA oral presentation
Magrolimab Is a Macrophage Checkpoint Inhibitor

- Magrolimab is an anti-CD47 monoclonal antibody that eliminates tumor cells through macrophage phagocytosis
- Magrolimab is being investigated in multiple cancers with >500 patients dosed

Magrolimab + Aza in Patients With MDS and AML: Study Design

Multicenter, single-arm phase Ib study

Current analysis reports data from expansion phase

Patients with untreated AML ineligible for induction CT or untreated MDS classed intermediate to very high risk by IPSS-R (N = 68)

Safety Evaluation

| Magrolimab 1, 30 mg/kg QW* + Aza 75 mg/m² Days 1-7 (n = 6) |

Expansion

| Magrolimab 1, 30 mg/kg QW or Q2W* + Aza 75 mg/m² Days 1-7 (n = 68) |

*Patients received magrolimab 1 mg/kg priming dose, followed by dose ramp-up to 30 mg/kg by Wk 2, continued thereafter.
AZA + Magrolimab: Response

<table>
<thead>
<tr>
<th>Best Overall Response, n (%)</th>
<th>First line AML (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>16 (64)</td>
</tr>
<tr>
<td>CR</td>
<td>10 (40)</td>
</tr>
<tr>
<td>SD</td>
<td>8 (32)</td>
</tr>
<tr>
<td>PD</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

Response per 2017 AML ELN criteria

ORR= overall response rate; CR= complete remission; SD= stable disease; PD= progressive disease
BiTE Antibodies in AML: Mechanism of Action and Targets

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD33</td>
<td>AMG330</td>
</tr>
<tr>
<td></td>
<td>AMG673</td>
</tr>
<tr>
<td>CD123</td>
<td>Flotetuzumab</td>
</tr>
<tr>
<td>FLT3</td>
<td>AMG427</td>
</tr>
</tbody>
</table>

Novel Combination Therapy in AML

- Sensitivity to single agents is genotype dependent
- AML is genetically highly heterogeneous
- **Thousands of genotype:drug pairs, even with a single drug**

Doublet or triplet combinations likely needed for maximum potency

However, with 20 drugs:
- 190 possible doublet combinations
- 1,140 possible triplet combinations
Summary

**Hypomethylator monotherapy** yields low CR rates, requires > 2 cycles to achieve best response, are not curative.

**Enasidenib**
used in outpatient setting may benefit older adults with de novo mutant-IDH2 AML who are not candidates for chemotherapy.

**Ivosidenib**
well tolerated
In advanced IDH1-mutated R/R AML, induces transfusion independence, durable remissions, and molecular remissions in some patients with CR.

**Venetoclax plus hypomethylators** show tolerable safety and favorable CR rates (67%) in elderly patients with AML. This novel combination regimen produced favorable responses in high-risk groups, such as age 75 or older, poor cytogenetics, and secondary AML.
Treatment of R/R AML

Relapsed or Refractory AML

Molecular studies, Cytogenetics and Immunophenotyping

- With or without actionable target
  - 1st relapse: young and/or fit*
  - 1st relapse: older and/or less fit, or PIF/ multiple relapses

- No actionable targets
  - FLT3- or IDH-mutated

Clinical Trial (If available)

- CR > 4 months or CR > 4 months with favorable/intermediate disease
- CR < 4 months with unfavorable disease

Cytotoxic Chemotherapy (MEC, FLAG-IDAC OR HIDAC)

Targeted Inhibitor**

HMA/LoDAC + Venetoclax†

- No target
- Actionable target

HMA/LoDAC + Venetoclax†

Targeted Inhibitor

Targeted Inhibitor

HMA/LoDAC + Venetoclax†

Targeted Inhibitor

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Conclusions

INDIVIDUALIZED TREATMENT FOR AML

❖ Flt-3 mutated AML: incorporate Flt-3 inhibitor to HMA
❖ IDH1/IDH2 mutated AML: incorporate inhibitor to HMA
❖ Venetoclax + HMA standard of care for those not candidates for IC
❖ Maintenance therapy required (with HMA?)
❖ Significant number of promising agents in development
❖ Combination therapy may further increase efficacy
❖ Oral combinations are warranted to improve quality of life

Future for AML treatment appears promising
ALL

Adele K. Fielding

Professor of Haematology
Group Leader UCL Cancer Institute

Former Chair, UK NCRI Adult ALL subgroup
Chair European Working Group on ALL
Aims and Objectives

• Overview of ALL – presentation and diagnosis and principles of treatment
• Prognosis in ALL – how do we determine risk?
• How do we choose a treatment strategy for an individual patient?
• Likely direction for future therapies
Normal blood cells

- Eosinophil
- Neutrophil
- Basophil
- Red blood cell
- Lymphocyte
- Monocyte
- Platelet

**Blood Count Details**

<table>
<thead>
<tr>
<th>Value</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>6.8</td>
</tr>
<tr>
<td>NE</td>
<td>52.6</td>
</tr>
<tr>
<td>LY</td>
<td>36.7</td>
</tr>
<tr>
<td>MO</td>
<td>7.8</td>
</tr>
<tr>
<td>EO</td>
<td>2.5</td>
</tr>
<tr>
<td>EA</td>
<td>0.4</td>
</tr>
<tr>
<td>RBC</td>
<td>5.29</td>
</tr>
<tr>
<td>HGB</td>
<td>16.2</td>
</tr>
<tr>
<td>HCT</td>
<td>47.0</td>
</tr>
<tr>
<td>MCV</td>
<td>88.8</td>
</tr>
<tr>
<td>MCH</td>
<td>30.7</td>
</tr>
<tr>
<td>MCHC</td>
<td>34.5</td>
</tr>
<tr>
<td>RDW</td>
<td>12.5</td>
</tr>
</tbody>
</table>

**Platelet**

- PLT: 179
- MPV: 8.4
What is ALL?

Bone marrow

Blood
Common presenting symptoms usually relate to lack of normal blood cells or general symptoms relating to accumulation of abnormal cells:

- Tiredness/fatigue
- Shortness of breath
- Recurrent infections
- Easy bruising or bleeding
- Petechiae
- Fever or night sweats
- Enlarged lymph nodes, liver or spleen
- Weight loss or loss of appetite
- Bone pain
- Shortness of breath
- Too few red cells
- Too few white cells
- Too few platelets
- Too many abnormal cells in the wrong place
- None

Can sometimes be discovered in routine testing
Acute Lymphoblastic Leukaemia - Diagnosis

Bone Marrow Aspirate and Trephine
Knowing how lymphocytes develop
Allows us to make diagnosis and do MRD
SEER data: Age-specific incidence of ALL

Less good outcomes
Prognosis and risk assessment
Biomarkers

A biomarker is a biological marker measurable in tissue, blood, or other body fluids, which is an indicator of some clinically significant condition.

Prognostic biomarkers correlate with the natural progression or aggressiveness of a disease.
for example t(4;11)

Predictive biomarkers are defined by their role in predicting a response to a given treatment.
for example MRD quantification
# Prognosis and risk assessment

## Table 1
Prognostic factors for adult acute lymphoblastic leukemia

<table>
<thead>
<tr>
<th>Factor</th>
<th>Detail</th>
<th>Selected References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At diagnosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Worse outcome with advancing age—no clear age cutoff in adults</td>
<td>11-14</td>
</tr>
<tr>
<td>Presenting white blood cell count</td>
<td>$&gt;30 \times 10^9/L$ (B), $&gt;100 \times 10^9/L$ (T)</td>
<td>11,13</td>
</tr>
<tr>
<td>Immunophenotype</td>
<td>In adults, T ALL can have a better outcome than B ALL</td>
<td>11,13,15,16</td>
</tr>
<tr>
<td>CD20 expression has been associated with a less good outcome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Poor: $t(9;22)$, $t(4;11)$, complex (&gt;5 abnormalities), low hypodiploidy near triploidy</td>
<td>17,18</td>
</tr>
<tr>
<td>Specific molecular abnormalities</td>
<td>JAK2, IKFZ1, PAX5</td>
<td>4,19-23</td>
</tr>
<tr>
<td>Response to therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid responsiveness</td>
<td>Response to steroids has clear relationship with outcome in childhood ALL. Less well defined and tested in adult ALL</td>
<td>24</td>
</tr>
<tr>
<td>Speed of initial response</td>
<td>Rapid initial response—CR within 4 weeks predicts better outcome. Not uniformly demonstrated.</td>
<td>25</td>
</tr>
<tr>
<td>Minimal residual disease</td>
<td>Clear relationship between MRD at protocol-specific time points and outcome in several studies</td>
<td>9,26-30</td>
</tr>
</tbody>
</table>
Genetic Subgroups of ALL

**Children**

- **B-lineage**
  - Hypodiploidy <45 chromosomes: 1%
  - Hyperdiploidy >50 chromosomes: 25%
  - TEL-AML1 t(12;21): 22%
  - BCR-ABL t(9;22): 3%
  - MLL rearrangements e.g. t(4;11), t(11;19), t(9;11): 8%
  - HOX11L2 5q35: 2%
  - TAL1 lp32: 6%
  - LYL1 19p13: 1.5%
  - HOX11 10q24: 0.5%
  - E2A-PBX1 t(1;19): 5%
  - MYC t(8;14), t(2;8), t(8;22): 2%

- **T-lineage**
  - Others: 24%

**Adults**

- **B-lineage**
  - Hyperdiploidy >50 chromosomes: 7%
  - TEL-AML1 t(12;21): 2%
  - E2A-PBX1 t(1;19): 3%
  - BCR-ABL t(9;22): 2%
  - Others: 26%
  - MYC t(8;14), t(2;8), t(8;22): 4%

- **T-lineage**
  - MLL rearrangements e.g. t(4;11), t(11;19), t(9;11): 10%
  - HOX11L2 5q35: 1%
  - LYL1 19p13: 12%
  - TAL1 lp32: 6%
  - HOX11 10q24: 6%
ALL: overall principles of treatment

Initiate immediate supportive management and consider patient preferences before chemotherapy e.g. TYA unit, older persons vs. intensity

Ensure specific diagnostic investigations that influence immediate management are done

e.g. BCR-ABL, TMPT status, G6PD status, imaging in case of extramedullary disease, LP if CNS disease suspected

Vital to take MRD specimen at diagnosis

Tissue-type patients/sibs at diagnosis even if not clear whether allo will be needed

Start steroid pre-phase

Chemotherapy = the mainstay of immediate upfront Rx for BCR-ABL neg

Targeted therapies increasingly important
ALL principles of chemotherapy

- ‘Induction’ to obtain “complete remission”
- CNS-directed prophylaxis (IT and HDMtx)
- Risk assessment
  - Response to induction
  - MRD
  - Other elements of risk - cytogenetic
- Decision re blin +/- alloHCT or continued chemo
- Intensification/consolidation
- Maintenance
Determinants of initial treatment response and OS in ALL

- Leukaemic cell properties
  - Tumor burden
  - Primary genetic lesion
  - Associated genetic lesions
- Host properties
  - Age
  - Comorbidities
  - Pharmacogenomics
- Microenvironment
  - Niche protection
  - Role in drug resistance
- Treatment
  - Drugs
  - Scheduling
  - Appropriate delivery
  - Drug interactions
  - Immunotherapies
  - Effector cells
- Response
- Toxicity
- OS
MRD - ways of measuring what we can’t see
Under the microscope

![Graph showing relative frequency of leukemic cells over follow-up time.](image)

- Detection limit of cytomorphology
- Detection limit range of flow cytometry
- Detection limit range of PCR technique

I-BFM-SG protocol I C II maintenance Rx
How to choose treatment for an individual outside a trial

- Age – child versus adult etc
- Co-morbidities which will affect tolerance of therapy
- What therapies are licensed and reimbursed
- Patient preference if there is a choice
**UKALL14: High risk**

- Presenting WBC $>30 \times 10^9/l$ B-cell OR $>100 \times 10^9/l$ T-cell)
- Age $>40$
- High-risk cytogenetic abnormalities:
  - t(9;22) ie Ph+
  - t(4;11)
  - Hypodiploidy/near triploidy
  - Complex (> 5 abnormalities)
- Standard-risk but **MRD positive** end of phase 2
How to decide on bone marrow transplant or not?

Risk of relapse is greater than the risk of suffering harm from the transplant
Blinatumomab: Bispecific T Cell Engaging (BiTE®) Antibody

Triggers expansion of BiTE-activated CD4 and CD8+ T cells, as long as drug is present and target cells persist.

Run-in dose for 1 week, then full dose for 3 weeks by continuous 24 hours infusion.

Up to 5 (monthly) cycles.
Inotuzumab ozogamicin: antiCD22-calicheamicin

3 doses d1,8,15
21–28 d cycle [≤6 cycles])
Can be given without in patient hospitalisation
Chimeric Antigen Receptor (CAR) T cells
Comprehensive interrogation of genetic & clinical relationships in adult acute lymphoblastic leukaemia: the translational cycle

A very successful clinical trial, UCL CTC sponsored

Complete

≈2500 (serial) patient specimens banked

Characterisation by cytogenetics, MRD analysis & post allograft multi-lineage chimerism

Ongoing CRUK program

Definition of new molecular subgroups

Genotype-Phenotype correlations

Multivariate risk stratification models

Strong new collaborations:

Fielding
Moorman
Papaemmanuil
Wrench

Future
Better trials, better science, better treatment
Aknowledgments

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• UK National Cancer Research Institute
• National Health Service Hospitals and staff, UK

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Richard Burt
Sara Aref
Dina Okasha
Rachel Mitchell
Krisztina Alapi
Callum Muirhead
SooWah Lee
Melanie Aguiar

UKALL14 Trial Management Group
Clare Rowntree
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Andrew McMillan
Tobias Menne

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Amy Kirkwood
Emma Lawrie
Amy Douglas
Pip Patrick

UCL CI
Marc Mansour and lab T-ALL

UCL CI/Infection and Immunity
Ron Chakraverty

MSKCC/Sanger
Elli Papaemmanuil
Peter Campbell

Past lab members
Christie Zhang
Bela Patel
Anna Castleton
Lena Rai

All of my dear leukaemia service colleagues at UCLH