Mixed lineage leukemia in AYA patients

Lymphoma Tumor Board

May 5, 2017
FIGURE 3
Age-specific incidence of ALL and AML, children and adults

**Children**
- Cases/1,000,000 children
- Bars for ALL and AML

**Adults**
- Cases/1,000,000 adults
- Graphs for ALL and AML

**Age (years)**
- 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19
Background

- Mixed-phenotype acute leukemia (MPAL) is rare
- Heterogeneous group of rare leukemias for which assigning a single lineage of origin is not possible
- Defined by limited set of lineage-specific markers
- Multipotent progenitor cells can differentiate into both myeloid and lymphoid lineages
- Factors possibly related:
  - Viral infection
  - Hereditary factors
  - Radiation exposure
  - Chemical exposure
- Association with several mutations, most common being t(9;22) and MLL gene rearrangement at 11q23
Adolescent and Young Adults with AML

• Acute Myeloid Leukemia (ALL) represents 33% of adolescent and 50% of adult leukemia.

• Diagnosis should be based on cytogenetic and molecular factors to avoid overtreatment.

• “Poorer prognosis of AYAs can be overcome with intensive pediatric protocols; whether a similar approach should be applied to AYAs with AML is not evidently provided.”

• Intensifying therapy or “one-size-fits-all” therapy does not improve survival rates.
Adolescent and Young Adults with ALL

• Acute Lymphoblastic Leukemia (ALL) survival rate is close to 90% for most children.

• In older adolescents and young adults (AYA), event-free survival is only 30-45%.

• Improved outcome, with disease-free survival rates of 60-70% are observed when AYA patients are treated with pediatric-based approaches.

• National Cancer Institute has defined the AYA population as those between the ages of 15 and 39 years.
Figure 1. T(9;22) translocation
Diagnosis

• Diagnosis requires >20% blasts in blood or marrow (or less in cases of chromosomal translocations and extramedullary presentation).
• “Sometimes the immature cells display cytochemical and/or immunophenotypic features of both lineages (biphenotypic) or there are different populations of leukemia cells (bilineal).”
• Symptoms due to bone marrow damage:
  • Bruising
  • Anemia
  • Persistent fever
  • Septicemia
• Symptoms due to leukemic cells infiltrating into tissues:
  • Lymphadenopathy
  • Joint pain
  • Swelling of the gums
  • Heptosplenomegaly
  • Headache/vomiting
  • Skin nodules or “lumps”
• Diagnosis cannot be based on morphology alone
Diagnosing criteria for BAL and MPAL

(A) EGIL criteria for the diagnosis of biphenotypic acute leukemia

(B) 2008 WHO criteria

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Ofir Wolach, and Richard M. Stone
Blood
2015;125:2477-2485
Distinguishing between AML and ALL using cytochemical stains

<table>
<thead>
<tr>
<th>Cytochemical Reaction</th>
<th>Cellular Element Stained</th>
<th>Blasts Identified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloperoxidase (MPO)</td>
<td>Neutrophil primary granules</td>
<td>Myeloblasts strong positive; monoblasts faint positive; Lymphoblast Negative</td>
</tr>
<tr>
<td>Sudan Black B (SBB)</td>
<td>Phospholipids</td>
<td>Myeloblasts strong positive; monoblasts faint positive; Lymphoblast Negative</td>
</tr>
<tr>
<td>Specific esterase</td>
<td>Cellular enzyme</td>
<td>Promyelocyte stage positive</td>
</tr>
<tr>
<td>Nonspecific esterase (NSE)</td>
<td>Cellular enzyme</td>
<td>Monoblasts strong positive; Others Negative</td>
</tr>
<tr>
<td>Periodic acid-Schiff</td>
<td>Glycogen and related substances</td>
<td>Lymphoblast's and pronormoblasts Negative to Positive; Myeloblasts usually negative; Metamyelocyte &amp; PMN Strong +ve</td>
</tr>
</tbody>
</table>
Distinguishing between AML and ALL using cytochemical stains (2)

<table>
<thead>
<tr>
<th></th>
<th>MPO</th>
<th>SBB</th>
<th>SPE</th>
<th>NSE</th>
<th>PAS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Myeloblasts</strong></td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>Diffuse</td>
</tr>
<tr>
<td><strong>Lymphoblasts</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-/+</td>
<td>Block</td>
</tr>
<tr>
<td><strong>Monoblasts</strong></td>
<td>++</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>Diffuse</td>
</tr>
</tbody>
</table>

a. Myeloblast: neg for all, M1 and up + MPO  
b. Lymphoblast: +PAS and acid phosphatase, +/- sudan black, neg for others  
c. Monoblast: strong + NSE, Lysozyme; neg to weak for MPO

![SBB](image1) ![MPO](image2) ![wright giemsa](image3) ![brown – a-naphtyl acetal esterase](image4) ![Blue is chloracetate esterase](image5)

Blue is chloracetate esterase
May-Grünwald-Giemsa–stained BM smear showing a mixed-cell population of large and small blasts

Estella Matutes et al. Blood 2011;117:3163-3171
Characteristic morphology

A

Wright-Giemsa

Periodic Acid-Schiff

Mycoperoxidase

B

SSCA

CD45

CD19

CD34

CD33

Dot plots with the blast population highlighted in blue (R1) and lymphocyte population in green (R2)

Dot plots with the blast population highlighted in red (R1) and lymphocyte population in green (R2)

Infinicyte band representation

MPAL case study (FHCRC): Bone marrow aspirate

RESULTS

[Scatter plots showing cell markers and distributions]
Immunophenotyping by flow cytometry after lysis of the erythroid cells reveals that the white blood cells consist of 51% blasts (CD34+), 6.8% maturing neutrophilic forms, 4.2% monocytes, and 30.5% lymphocytes. The lymphocytes consist of 20.0% B cells (CD19+), 63.5% T cells (CD3+) having a CD4:CD8 ratio of 3.3, and 16.5% NK cells (CD3-, CD7+).
Treatment

• Optimal treatment is still undefined as MPAL is quite rare
• Treatment based on:
  • Patient age
  • Medical history
  • Comorbidities
  • Blast morphology
  • Cytogenetics
  • Immunophenotype
  • Molecular studies
• Patients with 11q23 are considered separate entities
• Critical to define the Ph\(^+\) patients so TKI can be added
• Most patients get either AML or ALL treatment
• AML induction: cytarabine, anthracycline
• ALL induction: prednisolone, dexamethasone, vincristine, asparaginase, daunorubicin
• Using both may be associated with superior outcome
Therapeutic approach in patients with MPAL

Mixed phenotype acute leukemia (MPAL)

MPAL with t(9;22)(q34;q11.2); BCR-ABL1?

Yes

Acute lymphoblastic leukemia – like chemotherapy

+ Tyrosine kinase inhibitor

CR?

No

- Reassess phenotype
- Assess for TKI resistance/change TKI as indicated
- Consider AML-like salvage

CR?

No

Clinical trial/targeted therapy

Relapse

Reassess phenotype

Yes

Allogeneic stem cell transplant

CR?

Yes

No

Clinical trial/targeted therapy

CR?

CR?

CR?

No

Consider pediatric inspired protocol if <40 years old (in which case transplant in first remission not generally indicated)

For example High-dose cytarabine and mitoxantrone (HAM).

Preventive/Supportive Care and Monitoring

• Allopurinol is recommended for the first 10 days of induction therapy to prevent hyperuricemia.

• Antimicrobial prophylaxis, antiviral and *Pneumocystis jiroveci* pneumonia prophylaxis throughout treatment.

• Fungal prophylaxis should include mold coverage throughout induction therapy.
  – Broader spectrum azole antifungals cannot be used with vincristine.

• Asparaginase-related toxicities
  – Asparaginase-related hypersensitivity reactions can occur in 20% of children and adults.
Treatment Regimens (1)

• Adult Regimens:
  – Intensive use of myelosuppressive agents:
    • Duanorubicin
    • Cytarabine
    • Cyclophosphamidine
    • Allogeneic stem cell transplantation (SCT)

• Pediatric Regimens:
  – Berlin-Frankfurt-Munster (BFM) backbone:
    • Glucocorticoids
    • Vincristine
    • Asparaginase
    • Early and Frequent CNS prophylaxis and prolonged maintenance therapy
Treatment Regimens (2)

• “3+7” continues to be the backbone of induction therapy.
  – (daunorubicin 60–90 mg/m²/day idarubicin 10–12 mg/m²/day or mitoxantrone 10–12 mg/m²/day) and seven days of cytarabine (100–200 mg/m²/day)

• AYA patients usually receive one or two cycles of induction therapy.

• Additional CNS therapy is routine in most pediatric protocols.

• Bone marrow assessment on the 7\textsuperscript{th} or 10\textsuperscript{th} day after completion of induction treatment.
Overall survival of MPAL patients

Estella Matutes et al. Blood 2011;117:3163-3171
FDA Approval of midostaurin (RYDAPT®)

- Approved on April 28, 2017 by U.S. Food and Drug Administration
- For treatment of AML patients who are FLT3 mutation-positive
- LeukoStrat CDx FLT3 Mutation Assay was also approved to be used in conjunction with midostaurin to test patients with AML
- Based on randomized trial of 717 patients with previously untreated FLT3+ AML
- Most common serious adverse reaction was febrile neutropenia occurring in 16% of patients
- Recommended dose of midostaurin in AML is 50mg twice daily with food on days 8 to 21 of each cycle of induction and consolidation chemotherapy followed by 50mg with food as a single agent for up to 12 months
An International Prospective Randomized (rand) P-Controlled Double-Blind Trial (CALGB 10603/RATIFY [Alliance])

Overall Survival
With Number of Subjects at Risk

Survival Probability

Midostaurin 1 360 221 178 77 0
Placebo 2 357 172 143 71 0

survival time (months)

Arm 1: Midostaurin 2: Placebo

An International Prospective Randomized (rand) P-Controlled Double-Blind Trial (CALGB 10603/RATIFY [Alliance])

Event-Free Survival
With Number of Subjects at Risk

An International Prospective Randomized (rand) P-Controlled Double-Blind Trial (CALGB 10603/RATIFY [Alliance])

Overall Survival, by FLT3 group, treatment arm

 FLT3 Group, Treatment arm
- FLT3-ITD<0.7, Midostaurin
- FLT3-ITD<0.7, Placebo
- FLT3-ITD>=0.7, Midostaurin
- FLT3-ITD>=0.7, Placebo
- FLT3-TKD, Midostaurin
- FLT3-TKD, Placebo

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References

- Background photo: [https://www.oriel.nhs.uk/Web/Content/images/sg2.jpg](https://www.oriel.nhs.uk/Web/Content/images/sg2.jpg)
- Jonathan Fromm, MD, PhD – University of Washington/Seattle Cancer Care Alliance
- [http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4470138/](http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4470138/)
- [http://www.cancer.gov/types/aya](http://www.cancer.gov/types/aya)