Mixed-Lineage & Biphenotypic Acute Leukemia
Lymphoma Tumor Board
Friday, September 30, 2016
Mixed-phenotype acute leukemia (MPAL) is rare. It is a heterogeneous group of rare leukemias where assigning a single lineage of origin is not possible. It is defined by a limited set of lineage-specific markers. Multipotent progenitor cells can differentiate into both myeloid and lymphoid lineages. Factors possibly related include viral infection, hereditary factors, radiation exposure, and chemical exposure. Association with several mutations, most common being t(9;22) and MLL gene rearrangement at 11q3.
Figure 1. T(9,22) translocation

Diagnosis

- Patients diagnosed have >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
  - Heptoslenomegaly
  - Headache/vomiting
  - Skin nodules or “lumps”
- Diagnosis cannot be based on morphology alone
Diagnostic 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
May-Grunwald-Giemsa–stained BM smear showing a mixed-cell population of large and small blasts

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

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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)

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

MPAL case study (FHCRC): Bone marrow aspirate
MPAL case study (FHCRC): Bone marrow aspirate

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

No →

CR?

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

Yes →

Allogeneic stem cell transplant

No →

CR?

- Clinical trial/targeted therapy

Relapse

Reasses phenotype

CR?

Yes →

CR?

No →

Yes →

CR?

No →

CR?

- Clinical trial/targeted therapy

CR?

- Reassess phenotype
- Consider AML-like salvage

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*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).*
Overall survival of MPAL patients

A  Survival: All patients

B  Survival by Age

C  Survival by Genetics

D  Survival by Therapy

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

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References


• https://en.wikipedia.org/wiki/Biphenotype_acute_leukemia

• Background photo: https://www.oriel.nhs.uk/Web/Content/images/sg2.jpg

• Jonathan Fromm, MD, PhD – University of Washington/Seattle Cancer Care Alliance