De Novo AML
Overview

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Acute Myeloid Leukemia

- Incidence/Prevalence
- Disease Categories (FAB vs. WHO)
- Risk Stratification
  - Age, cytogenetics, molecular markers
- Induction/Consolidation Options
- Response Criteria
- Role of Clinical Trials
AML Fast Facts

- In 2008...
  - 13,290 new cases
  - 8820 deaths

- In comparison...
  - Lung cancer-220,000 new cases and 160,000 deaths
  - Pancreas 42,000 new cases and 35,000 deaths
  - Lymphoma-65,000 new cases and 19,000 deaths

- Relatively rare, but devastating disease for which new, less toxic therapies are needed

Median age 70 years

Tallman, M. S. Hematology 2005;2005:143-150
Clinical Features

- Infections, fatigue, dyspnea, bleeding, constitutional symptoms
- Elevated white blood count with circulating blasts (highly variable numbers)
- Anemia, thrombocytopenia
Diagnostic Workup

- Bone marrow aspirate/biopsy
  - Cytochemistry
  - Immunophenotyping
  - Cytogenetics—strongest prognostic factor
- Molecular testing
  - FISH for specific genetic rearrangements
  - PCR-based testing for
    - FLT-3
    - NPM1
    - CEBPA
  - More to come…
Disease Categories

- **FAB (French-American-British) classification**
  - Established in 1976
  - Based on morphology and cytochemical stains and flow cytometry
  - M0, M1, M2, M4, M5, M6, M7
  - M3 (acute promyelocytic leukemia)
  - 30% blasts in BM
WHO Classification

- Devised in 1999, revised in 2008
- Takes into account molecular changes, cytogenetics, evidence of dysplasia that are known to impact prognosis
- 17 subclasses of AML (!)
- 20% blasts in bone marrow required (not 30% as before)
WHO Categories

- AML with recurrent genetic abnormalities
  - \(t(8;21),\ inv(16)\) are CBF leukemias, have better prognosis
  - \(t(15;17)\) is APL (formerly M3) and is treated differently
- AML with myelodysplasia-related changes
- Therapy-related myeloid neoplasms
- AML, not otherwise specified
- Myeloid sarcoma
- Myeloid proliferations related to Down syndrome
- Blastic plasmacytoid dendritic cell neoplasm
Prognostic Factors

- Age

- Cytogenetics
  - Good
  - Intermediate
  - Poor

- Molecular markers
  - NPM1: Mutation is good
  - FLT-3: Internal tandem duplication mutation is bad
  - CEBPA: Mutation is good
  - New studies are often being published

- Response to therapy
  - Refractory leukemia is a bad prognostic sign
Age as a Risk Factor

B: Patients < 55 years old

C: Patients > 55 years old

Tallman M et al. Blood 2005. ECOG Data
Cytogenetics

- Better risk: inv(16), t(8;21)
- Intermediate risk: Normal, +8, t(9;11)
- Poor risk
  - Complex (>3 abnormalities)
  - -5
  - -7
  - 5q-
  - 7q-
  - Involvement of 11q23 (MLL)
  - inv(3) or t(3;3)
  - t(6;9)
Cytogenetics

Heterogeneity of 3 Groups: $P < .001$

Slovak M. Blood 2000. SWOG Data
Principles of Therapy for Patients < 60 years (or up to 75 years if fit)

- **Induction therapy**
  - Clear marrow blasts and restore normal hematopoiesis
  - “7+3” cytarabine infusion (7 days) plus anthracycline (daunorubicin or idarubicin) for 3 doses
- **Supportive care until count recovery**
  - Blood product transfusion
  - Infection management
  - Mucositis and need for nutritional support
Daunorubicin Dose

Fernandez, NEJM, 2009 from ECOG 1900 Study
Induction supportive care

- Antifungal and antiviral therapy
- Blood products
  - Leukoreduced
  - Irradiated
  - PRBCs for hemoglobin < 8, platelets for <10K
- Tumor lysis syndrome prevention
  - Hydration
  - Allopurinol
- Consider LP for WBC > 100,000, for symptoms or for monocytic histology
Principles of Therapy for Patients < 60 years (or up to 75 years if fit)

- **Consolidation therapy**
  - Required, as leukemia will relapse if not given
  - **Better risk:**
    - High dose cytarabine (HiDAC)
    - Clinical trial
  - **Intermediate risk:**
    - Matched sib allo SCT
    - HiDAC
    - Clinical trial
  - **Poor risk:**
    - Clinical trial
    - Matched sib allo SCT
    - Alternative donor SCT (cord blood or haplo donor)
Response Criteria for AML

- **Complete remission**
  - Bone marrow with <5% blasts
  - ANC >1000
  - Platelets >100,000
  - No extramedullary disease

- **Patients not in CR are considered to have failed treatment**

- **Bone marrow assessed at ~day 14 and again at count recovery**
Response Criteria for AML

- Partial remission
  - Decrease of at least 50% in the blast percentage (to 5-25%) in bone marrow
  - Normal peripheral blood counts

- Relapse
  - Reappearance of blasts in the peripheral blood or > 5% in the bone marrow after achievement of CR
Principles of Therapy for Patients > 60 years or unfit for intensive chemo

- Age 60-75 and good PS (ECOG 2 or better)
  - Good risk cytogenetics
    - Clinical trial
    - 7+3
  - Complex cytogenetics
    - Clinical trial
    - SQ cytarabine
    - Hydroxyurea
    - Best supportive care

- Age >75 or PS >2 or organ dysfunction
  - Clinical trial
  - SQ cytarabine
  - Hydroxyurea
  - Best supportive care
Consolidation Options for Patients >60

- Clinical trial
- Reduced intensity allo transplant for those with suitable donors and who are fit
- Cytarabine
- Best supportive care
Pathogenesis

- Class I mutations increase proliferation/survival
  - FLT3
  - RAS
  - KIT

- Class II mutations lead to impaired differentiation
  - Core binding factor (RUNX1, CBFB-MYH11)
  - PML-RARa in APL
  - MLL rearrangements involving 11q23

- AML requires one of each type of mutation
Pathogenesis

Therapeutic Targets in Leukemia

Proliferation/survival mutations, do not affect differentiation
- FLT3-ITD
- Oncogenic RAS
- KIT alleles
- PTPN11

Mutations associated with impaired differentiation, self-renewal
- Core binding factor (CBF)
- Retinoic acid receptor α
- MLL rearrangements
- Co-activators (CBP, TIF2)
- RUNX1, GATA-1, C/EBPalpha

FLT3 inhibitors
- Others

Acute Leukemia

ATRA
- ?HDAC inhibitors

Targeting self-renewal: WNT, Notch, BMI-1, HOX
Developmental Therapeutics

- “7+3” has been used for 30 years with results as shown
- Transplant is improving, but is not for everyone
- Many challenges
  - Relatively rare disease
  - Molecular diversity
  - Patients often have co-morbidities
  - Treatment often needs to start quickly
    - Risk stratification
    - Randomization
Targets and Possible Therapies

- **Signal transduction**
  - FLT3: Small molecule inhibitors
  - RAS: Farnesyl transferase inhibitors
  - mTOR: Rapamycin
  - PI3/AKT: Small molecule inhibitors

- **Differentiation**
  - PML-RARa: ATRA, arsenic for APL
  - CBF: HDAC inhibitors
  - MLL fusions: HDAC inhibitors, hypomethylating agents

- More targets will be coming
- Adaptive randomization trial design
Questions/Discussion