Welcome and Introduction

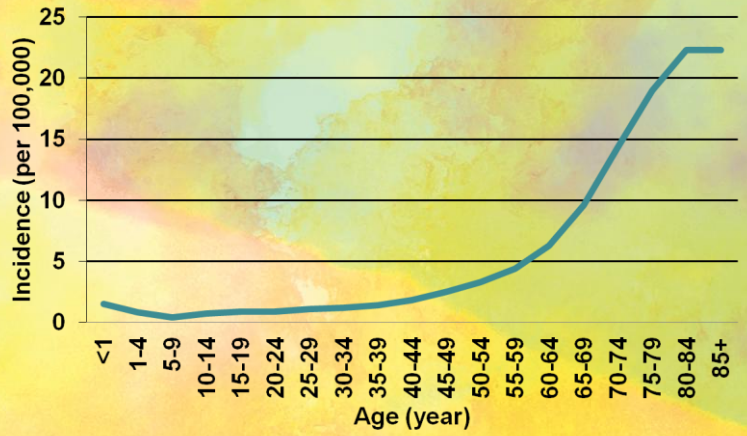
Clare Karten, MS
Senior Director, Mission Education
The Leukemia & Lymphoma Society

AML – Emerging Treatment Strategies

Wendy Stock, MD
Professor of Medicine, Section of Hematology/Oncology
Director, Leukemia Program
The University of Chicago Medicine
Chicago, IL

AML: Epidemiology

Incidence of AML Increases With Age



Available at: http://seer.cancer.gov/csr/1975_2009_pops09/browse_csr.php?section=13&page=sect_13_table.13.html. Accessed July 17, 2012.

Acute Leukemia

- Arises from a single transformed hematopoietic stem cell – "clonal"
- Characterized by block in normal blood cell maturation and growth advantage
- Very heterogeneous group of diseases
- Often defined by recurring abnormalities of chromosomes within leukemic stem cell

Clinical Features of Acute Leukemia

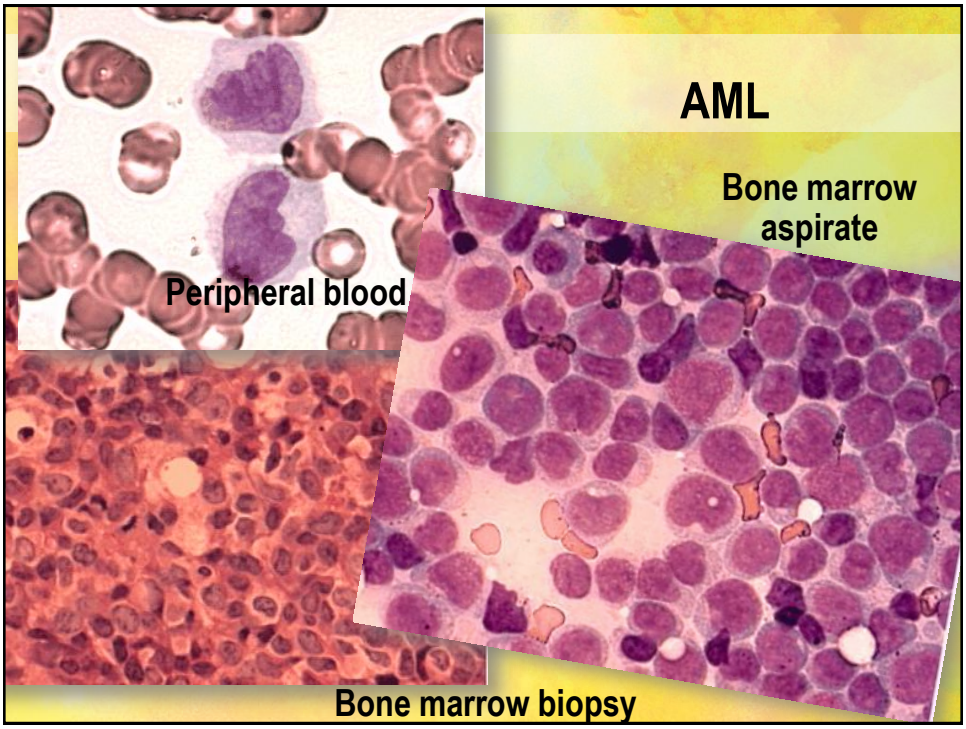
- **Fatigue, easy bruising, pallor**
- **Fevers**
- **Result from maturation arrest of blood cell development**
  - Anemia
  - Thrombocytopenia (low platelets)
  - Neutropenia (absence of normal granulocytes)

Goals of Treatment for Acute Leukemia

- **Eradication of malignant clone**
  - Combination chemotherapy
    - Based on semi-selective killing of rapidly dividing cells
  - New strategies involve development of drugs that specifically "target" abnormalities unique to the leukemia population
- **Restore normal hematopoiesis (normal blood cell growth and development)**

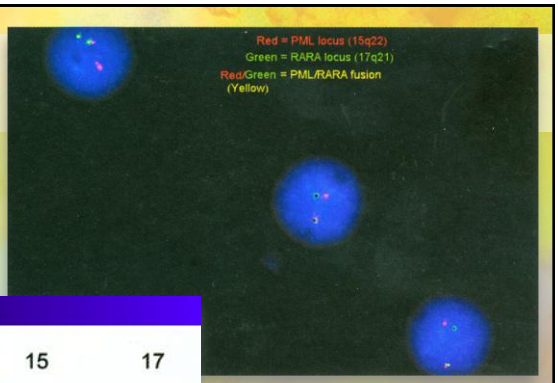
Diagnostic Work-up

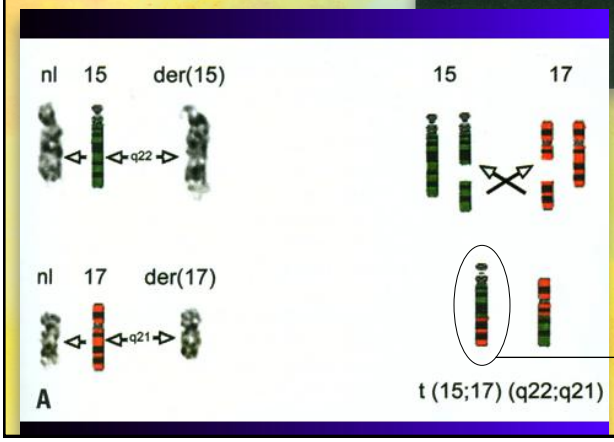
- **Examination of blood smear**
- **Bone marrow examination**
- **Immunophenotyping**
  - Identifies proteins on cell surface that are present in AML
- **Cytogenetics/FISH**
  - Identify chromosome rearrangements and deletions
- **Molecular diagnostics: Identify mutations**
  - *PML-RARA* in acute promyelocytic leukemia
  - *FLT3*, *NPM1*, *CEBPA*
  - Future: *IDH1*, *IDH2*, *TET2*, *DNMT3A*, *WT1*
- **Patients who might be considered for transplant should have HLA-typing done at time of diagnosis**



APL

Cytogenetics/ Molecular Diagnosis





Fusion Gene = *PML-RARA*

Ancillary Testing/Services

- **MUGA scan**
- **Placement of indwelling tunneled catheter**
  - HICKMAN (triple lumen) typically used
  - Apheresis catheter (larger lumens) if considering autologous stem cell collection
- **Pretreatment CT scan sinus, high resolution CT chest can be considered**
- **Dental examination**
- **Provera for menstruating females**
- **Discuss fertility issues**

Supportive Care Critical

- **At diagnosis: DIC panel, LDH, uric acid**
- **Careful hydration, allopurinol**
  - Rasburicase (urate oxidase) to prevent tumor lysis
- **Judicious use of blood, platelet transfusions**
  - Typically, maintain Hgb >8 gm/dl
  - Platelets >10 K
- **Hematopoietic growth factors may be useful**
  - G-CSF

Infections

- **Prophylaxis during neutropenia: Data supportive for prophylaxis**
  - Antibacterial: Avelox® (moxifloxacin)
  - Antifungal: Diflucan® (fluconazole) or voriconazole in high-risk pts
  - Consider anti-viral if HSV+: Acyclovir 400 mg/day
  - PCP prophylaxis in ALL, CLL
- **Treatment of neutropenic fever**
  - Based on source, if possible:
    - Ceftazidime, meropenem, vancomycin
    - Voriconazole, posaconazole, AmBisome® (amphotericin), micafungin

AML: Epidemiology

Risk Factors

Genetic Disorders	Down syndrome Neurofibromatosis Klinefelter syndrome Shwachman syndrome	Patau syndrome Fanconi anemia Kostmann syndrome
Physical & Chemical Exposures	Benzene Pesticides Cigarette smoking	Embalming fluids Herbicides
Radiation Exposure	Both therapeutic and nontherapeutic radiation	
Chemotherapy	Alkylating agents Topoisomerase-II inhibitors • Anthracyclines • Epipodophyllotoxins Taxanes	

Deschler B, Lübbert M. *Cancer.* 2006;107:2099-2107.

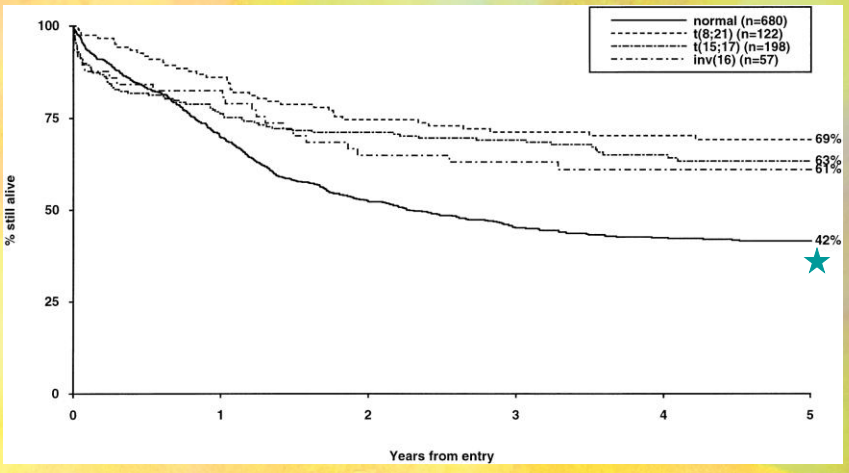
How Do We Treat AML?

- **Most active traditional chemotherapy drugs:**
  - Cytarabine – purine analog
  - Anthracycline: daunorubicin, idarubicin, mitoxantrone
  - Other agents with activity: etoposide
- **Agents often given in combination: "7+3"**
- **Induction therapy to achieve "complete remission"**
- **Post-remission chemotherapy**

Post-Remission Therapy for Acute Leukemia: Several Options

- **Additional courses of chemotherapy are required for eradication of disease**
  - "Consolidation of remission"
  - May cure good-risk patients
- **Intensification with hematopoietic stem cell transplantation**
  - Autologous (patient's own stem cells)
  - Allogeneic (donor stem cells)
  - May improve outcome of higher risk patients

Cytogenetics is Important Prognostic Factor in AML



Grimwade D et al. *Blood.* 1998;92:2322-2333.

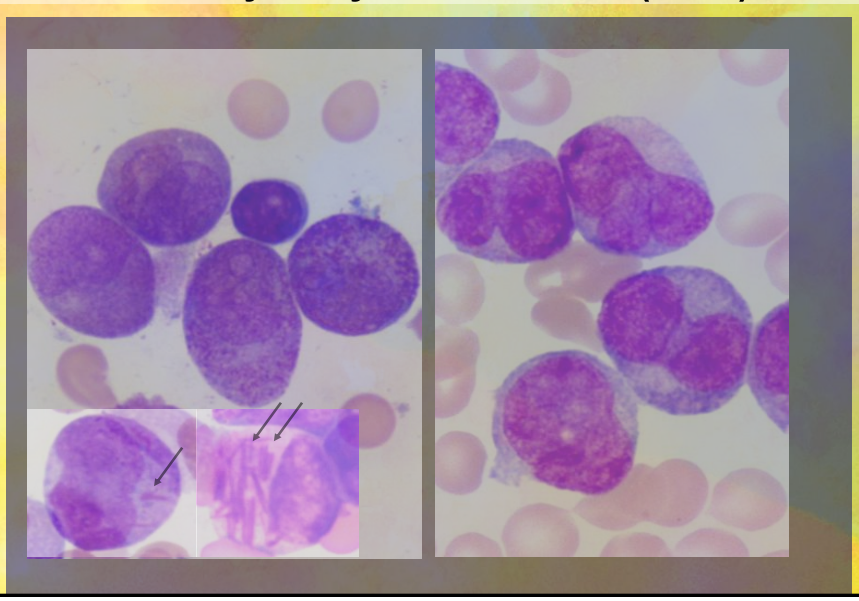
Looking Towards the Future

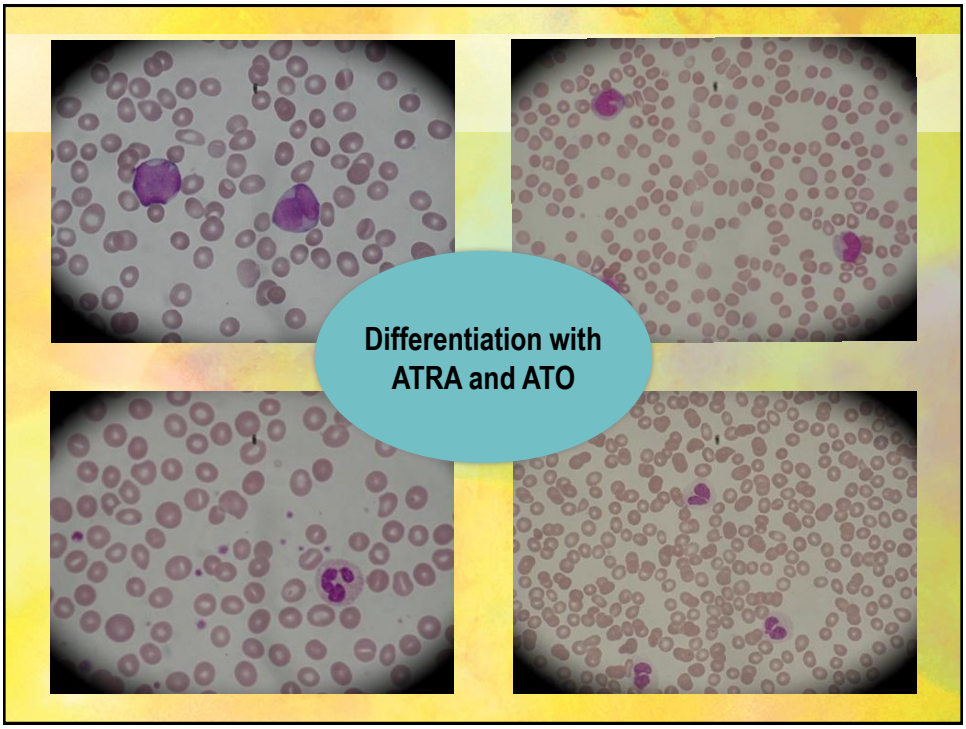
- How can we incorporate insights of disease biology into treatment?
- 3 examples…

Acute Promyelocytic Leukemia

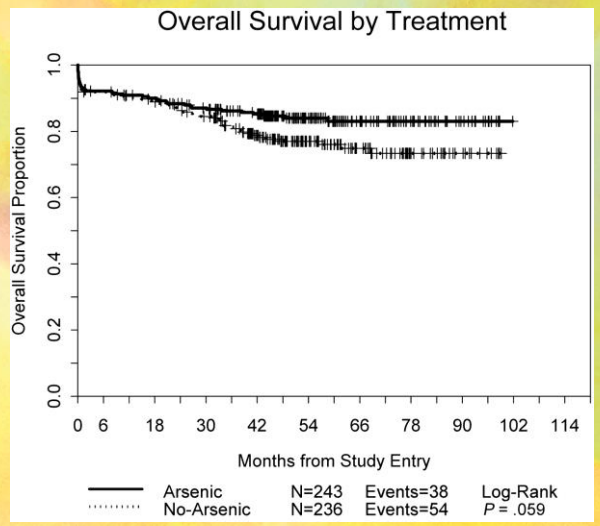
- Must identify this subset at diagnosis
- Treatment directed at molecular abnormality resulting from t(15;17), the *PML-RARA* fusion gene
  - Results in abnormal signaling through retinoic acid receptor
- ATRA (all-trans retinoic acid) incorporated into treatment with standard AML chemotherapy now results in cure of majority of patients!
  - Addition of arsenic trioxide to frontline therapy improves outcome
- Arsenic trioxide as sole therapy results in prolonged remissions in good-risk patients

Acute Promyelocytic Leukemia (cont)



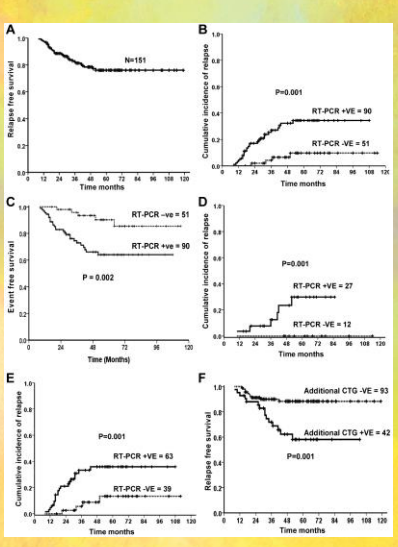


ATRA + Chemotherapy + Arsenic Trioxide Results in Excellent Overall Survival for Adults with APL



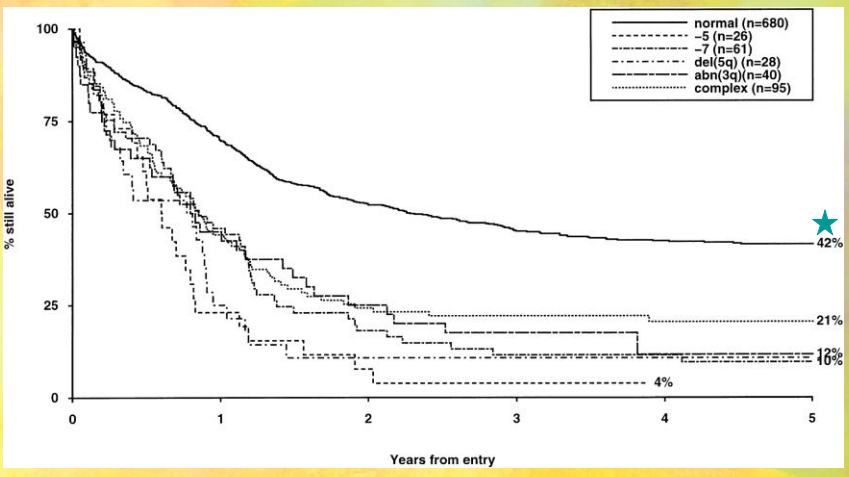
Powell BL et al. *Blood.* 2010;116:3751-3757.

Arsenic Trioxide as Sole Treatment for APL: Successful Approach for Good-Risk Disease



Chendamarai E et al. *Blood.* 2012;119:3413-3419.

Cytogenetics as a Prognostic Indicator in AML



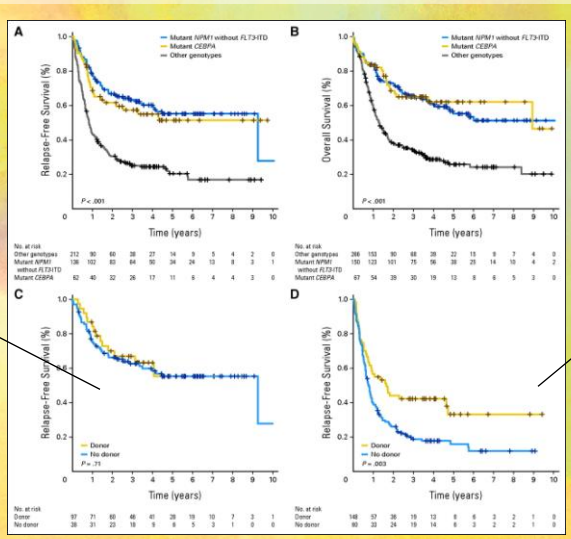
Grimwade D et al. *Blood.* 1998;92:2322-2333.

FLT3 Mutations in AML

- ***FLT3*** **is a tyrosine kinase critical to normal myeloid cell growth and development**
- ***FLT3*** **mutations occur in 20-30% of adults with AML**
  - Occurs in all age groups
  - Most common in AML with a normal karyotype
- **Remission rates are quite high; but early relapses occur with standard AML chemotherapy**

Molecular Genetics of AML With Normal Karyotype: Transplant in CR1?

NPM1 and *CEBPA* mutations respond to chemotherapy



FLT3 mutant group may benefit from transplant in CR1

Marcucci G et al. *JCO.* 2011;29:475-486.

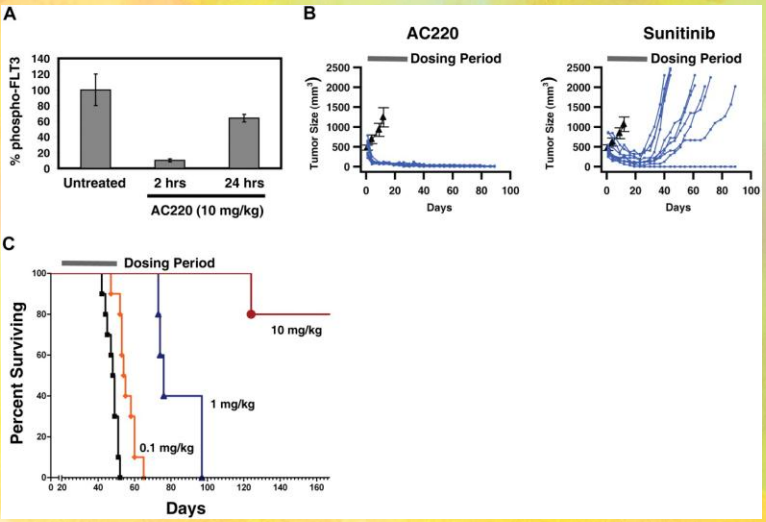
Targeting *FLT3*: Use of TKIs

- **Multiple TKIs have been tested and demonstrate some single agent activity with target inhibition:**
  - Sorafenib
  - Midostaurin
  - AC220 (quizartinib)
- **Recently completed international trial C10603 testing benefit of midostaurin + chemotherapy in adults <60 years with *FLT3* mutant AML**
  - Randomized phase III trial
  - Trial results pending

Current *FLT3* Inhibitor Trials

- **Combination trial for frontline treatment in older adults with *FLT3* mutations**
  - Combining chemotherapy with sorafenib
    - Ongoing trial in the Alliance
- **Most active agent to date may be AC220**
  - Currently in expanded phase II studies of two different doses for patients with relapsed AML
    - Multi-center trial just opened

In Vivo Efficacy of AC220 in Animal Tumor Models

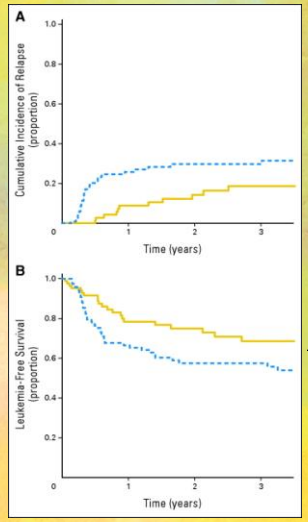


Zarrinkar PP et al. *Blood.* 2009;114:2984-2992.

FLT3 Mutant AML: Treatment Recommendation

- Screen for *FLT3* mutation at time of diagnosis
- HLA typing should be done at diagnosis
- Enroll on frontline clinical trial that incorporates *FLT3* inhibitor trial with chemotherapy
- Consider allogeneic stem cell transplant in first remission
- Clinical trials with new inhibitors for relapse such as quizartinib or other

Outcome After Allogeneic Transplantation Performed in First Complete Remission for Patients With Acute Myeloid Leukemia And Normal Cytogenetics According to the Presence (Dashed Line) or Absence (Solid Line) of Internal Tandem Duplication of *FLT3* Gene

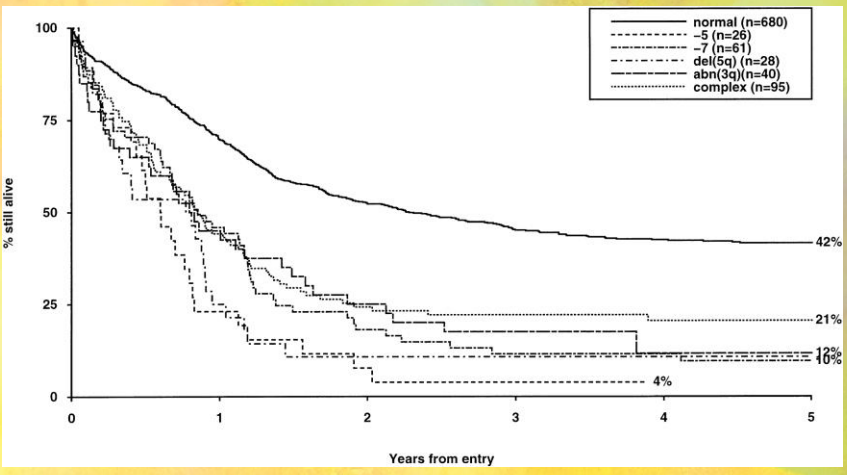


FLT3 mutated AML also benefitted from allo-SCT

Brunet S et al. *JCO.* 2012;30:735-741.

JOURNAL OF CLINICAL ONCOLOGY

Cytogenetics as a Prognostic Indicator in AML



Grimwade D et al. *Blood.* 1998;92:2322-2333.

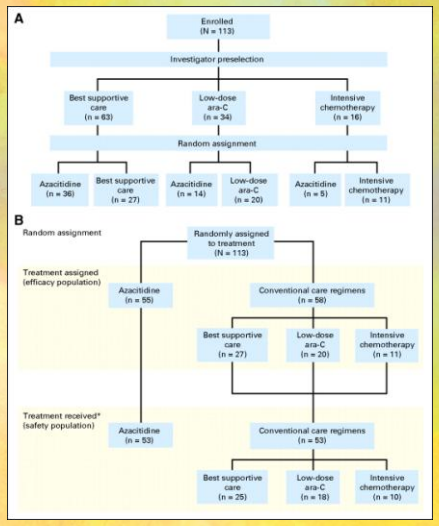
Poor-Risk AML: What is New?

- **Biology and age often coincide in AML**
  - Poor-risk disease and older age associated
- **Often associated with AML that arises from a preceding myelodysplastic syndrome or myeloproliferative disease**
- **Standard cytotoxic chemotherapy has not been an effective strategy**

The Epigenome and AML

- Regulation of myeloid development
- Evidence for abnormal methylation/silencing of genes that are critical for normal myeloid development
- Multiple studies suggest that use of drugs that may regulate epigenome may be effective
  - Vidaza® (5-azacitidine)
  - Dacogen® (deoxycytidine)
  - Histone deacetylase inhibitors (vorinostat)

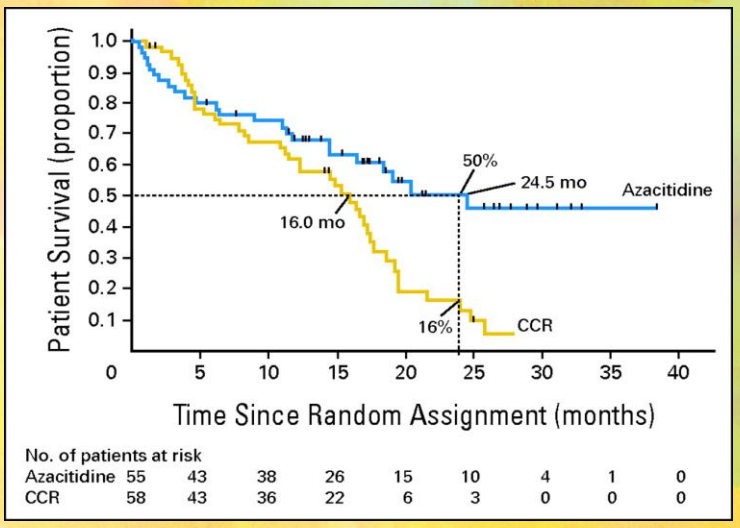
AML in Patients With Low Blast Percentage: Vidaza vs Investigator Chosen Therapy



Fenaux P et al. *JCO.* 2010;28:562-569.

JOURNAL OF CLINICAL ONCOLOGY

Kaplan-Meier Plot of Overall Survival in Patients Receiving Azacitidine (n=55) or Conventional Care Regimens (CCR; n=58)



Fenaux P et al. *JCO.* 2010;28:562-569.

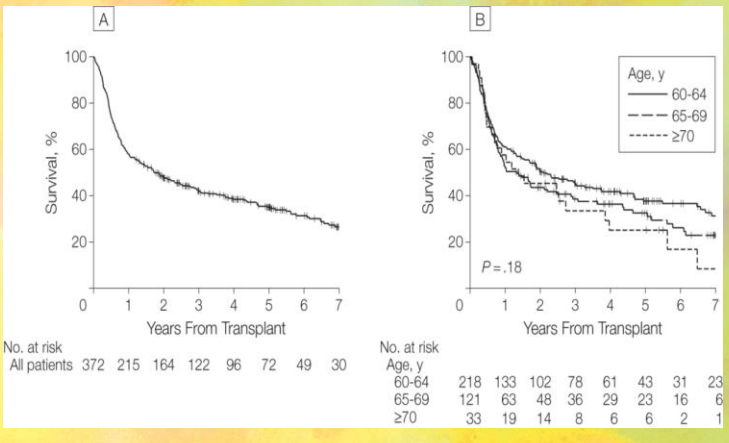
Decitabine: Prolonged Exposure Better?

- **Decitabine was given for 10 days at dose of 20 mg/m^2 to older adults with untreated AML**
  - Median age was 74 years
- **Complete remission was achieved in 50% of patients after median of 3 cycles**
  - Patients with both normal and poor-risk cytogenetics responded

Ongoing or Planned Trials for High-Risk/ Older Patients

- A recently activated Alliance phase II trial in previously untreated older AML patients randomized to decitabine (x10 days) versus decitabine plus bortezomib (subcutaneous) (Alliance 11002)
  - Based on intriguing data that bortezomib can enhance decitabine activity
    - miR-29b upregulation
- ECOG trial: Evaluating clofarabine (another active agent) in older adults with AML
- SWOG trial: Azacitidine + Mylotarg® (gemtuzumab ozogamicin, a monoclonal antibody)

Allogeneic Transplant Can Result in Prolonged Survival in Patients >60 Years Old



From: "Long-term Outcomes Among Older Patients Following Nonmyeloablative Conditioning and Allogeneic Hematopoietic Cell Transplantation for Advanced Hematologic Malignancies"

Sorror ML et al. *JAMA*. 2011;306:1874-1883. doi:10.1001/jama.2011.1558.

Older Adults with AML: Suggestions

- **Standard treatment with chemotherapy may benefit only limited numbers of older adults with AML**
  - Critical to identify good-risk as well as bad-risk patients at diagnosis to make optimal choice
    - Molecular diagnostics and cytogenetics critical
- **Consider enrollment on clinical trial – many available currently**
- **HLA type at diagnosis: transplant has the potential for cure, even in older adults**
  - Consider referral for transplant consultation in CR1

Conclusions

- **AML treatment increasingly dependent on underlying biology of the disease**
- **Crucial to obtain the proper diagnostic work-up to allow appropriate treatment selection**
- **Biologically targeted agents provide potential for significant improvements in outcome**
- **Allogeneic transplant in first remission recommended for high-risk groups**
- **CLINICAL TRIAL ENROLLMENT: PATH TO CURE!**

Question & Answer Session

LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

LLS Support

LLS is funding AML research at many sites across the US and Canada

For more information about AML and other LLS programs, please contact an LLS Information Specialist

- **TOLL-FREE PHONE: (800) 955-4572**
- **EMAIL:** infocenter@lls.org

For resources such as free education materials, past programs, webcasts and more, visit www.LLS.org/resourcecenter.