

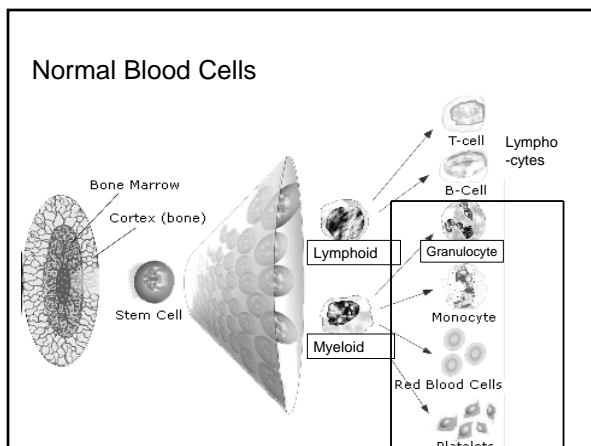
Tomorrow's Therapies Today: *Clinical Trials for* Leukemia, Lymphoma & Myeloma

**Evolving Therapies in
Acute Adult Leukemias**

Selina M. Luger, MD
*Associate Professor of Medicine
Hospital of the University of Pennsylvania
Philadelphia, Pennsylvania*

Leukemia

- 19th century European physicians noted a disorder of elevated white blood cells
 - "leukos"=white, "haima"=blood
- Leukemia
 - Cancer of the bone marrow which is the organ for normal blood cell development
 - Results in uncontrolled growth of abnormal blood forming cells in the bone marrow which affects the number of normal cells in the blood
 - 35,000 new cases in U.S./year
 - 90% in adults
 - 10 times more often in adults than in children
 - Incidence of leukemia has decreased by 1.1% each year since 1995
 - Myelogenous vs. Lymphoid
 - Acute vs. chronic



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Acute Leukemia

- Normal Bone Marrow
 - Has all of the types of cells necessary to make the blood cells needed in the bloodstream and body
 - <5% blasts in normal bone marrow
 - Cells mature in the bone marrow and then enter the blood and carry out their functions. Uncontrolled proliferation of a malignant clone of immature hematopoietic cells
- Acute Leukemia
 - 20% bone marrow cells are blasts
 - Transformed cells incapable of normal differentiation
 - Leukemic cells prevent the maturation and differentiation of other bone marrow cells.
 - Disease progresses rapidly and is fatal without treatment.

Acute Lymphocytic Leukemia (ALL)

- Acute leukemia where blasts are lymphoid in origin
- 3000–5000 new cases per year in US
- 20% of adult leukemias
- 75% of childhood leukemias
 - Childhood cancer is leading non-accidental cause of death in children
 - Most common childhood malignancy
 - Peak age is 4 years old

Acute Myelogenous Leukemia (AML)

- Acute leukemia where >20% of the bone marrow cells are non-lymphoid blasts
- The most common type of leukemia diagnosed in adults
 - 80% of adult leukemias
 - 11,000 cases per year

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Acute Leukemia – Bone Marrow Studies

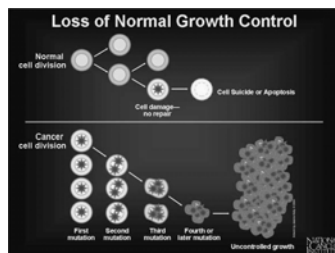
- Morphology – look at the cells to try and determine what type of leukemia it is
- Immunohistochemistry – stain the cells with substances that are specific for specific types
- Immunophenotype – look for proteins on the cell surface that help us identify the cell type
- Cytogenetics – analysis of chromosomes in the leukemia cells
- Diagnostic
- Prognostic

Chromosomes and Cancer

- It is possible for the DNA in some cells to get damaged over time.
 - Certain things are known to damage DNA.
 - Excessive radiation – eg, atomic bomb
 - Chemotherapy
 - Benzene
 - Other times, DNA is damaged without any clear reason.
- With damage to the DNA, the chromosomes can become abnormal.
- The cells that contain the abnormal DNA and chromosomes can become cancerous and grow uncontrollably.

Principles of Leukemogenesis

- A multistep process
- Dysregulation of cell growth and differentiation (associated with mutations in DNA)



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Acute Leukemia – Treatment Stages

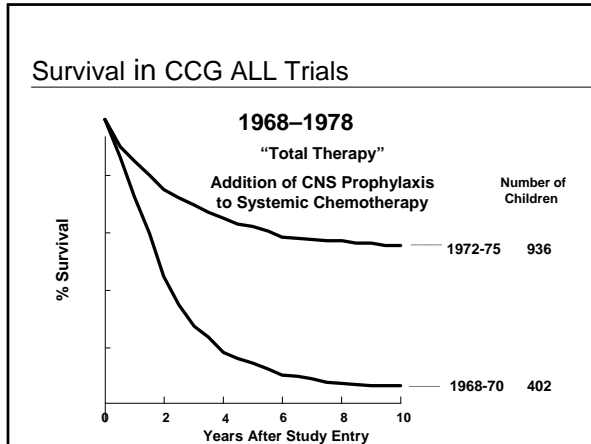
- Remission Induction
 - Initial goal of treatment is complete remission.
 - No evidence of leukemia
 - Return of normal bone marrow and blood cells
- Postremission Therapy
 - Prevent relapse of disease
- Salvage Therapy

Types of Postremission Therapy

- Chemotherapy that is similar to, but less intensive than, the initial chemotherapy
- Bone marrow transplantation
 - Use of high doses of chemotherapy +/- radiation to kill the patients' bone marrow followed by an "infusion of stem cells"
 - Autologous stem cell transplant
 - Allogeneic stem cell transplant
- Maintenance – low-dose, long-term chemotherapy

History of ALL Therapy

- 1940s: single agent chemotherapy
- 1950s: combination chemotherapy
- 1960s: maintenance chemotherapy, first group of children cured
- 1980s: induction followed by consolidation followed by reinduction and reconsolidation



Adult ALL

- Remission induction successful in >70% of patients
- CNS prophylaxis is now standard
- Chance of long-term, disease-free survival (ie, no relapse) is best if a bone marrow transplant is done from a HLA-identical sibling in first remission.

ECOG E2993/MRC UKALL XII (E2993)

- Induction chemotherapy for 2 months
- If in CR, 1 more month of chemotherapy
- Assignment/randomization
 - If allo sibling available and under age 50 – allo transplant
- Older or no allo sibling – randomize to autologous transplant vs standard chemotherapy x 2 1/2 years

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Risk Definitions

- Standard Risk
 - Age <35
 - Not have a very high white blood cell (WBC)
- High Risk
 - Age 35 or over OR
 - Elevated WBC
 - Philadelphia chromosome positive

E2993 5-year Data

	N	Survival (%)	Relapse (%)
DONOR	388		41
High Risk	170	39	32
Standard	218	63	25
NO DONOR	527	45	54
High Risk	230	36	63
Standard	286	51	48

E2993 – Ph negative

- High induction remission rate in adults with ALL
- Standard-risk patients with sibling donor benefited from allogeneic transplant in CR1
- High non-relapse mortality associated with allogeneic transplant in patients over age 35
- Patients receiving chemotherapy had better outcomes than those receiving a single autologous transplant without maintenance.

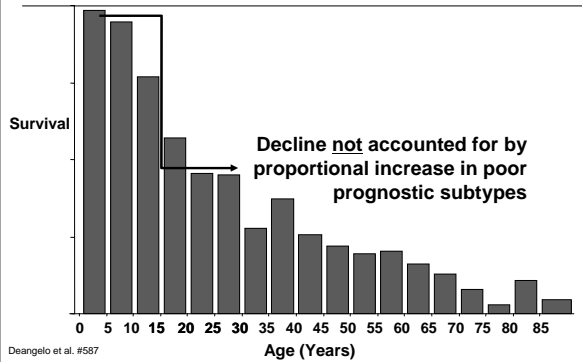
Rowe et al. ASH 2006

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ALL Questions

- What about Ph positive patients?
- Can we make transplant safer?
- Is there any group of patients that doesn't need therapy that is so aggressive?
- Can we get the benefit of transplant without the risk?

5-year Survival ALL 1975–1998 and Age



AYA with ALL on Pediatric vs. Adult Clinical Trials

Cooperative Group	Study Period/ No. Pts.	Age (yrs)	CR (%)	DFS (%)
North America (Stock)	1988–1998	16–21		(6-year)
CCG (peds)	196 pts		96%	64%
CALGB (adults)	103 pts		93%	38%
French (Boissel)	1993–1994	15–20		(5-year)
FRALLE (peds)	77 pts		94%	67%
LALA (adults)	100 pts		83%	41%
Dutch (deBois)	1985–1999	15–21		(5-year)
SKION (peds)	47 pts		98%	69%
HOVON (adults)	73 pts		91%	31% / 46%
Italian (Testi)	1996–2000	14–18		(2-year)
AIEOP (peds)	153		94%	83%
GIMEMA (adults)	95		95%	55%

Deangelo et al. #587

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DFCI Adult ALL Trial

- Regimen based on DFCI Pediatric Consortium Trial 00-01
- Objectives
 - To determine the feasibility and toxicity of the DFCI pediatric regimen in adult patients age 18 and older with ALL
 - To determine the proportion of patients who are able to complete the post-induction asparaginase therapy

Preliminary results

- Regimen appears feasible.
- Response and survival data are encouraging.
- Larger, multicenter study will need to be done to evaluate role of pediatric regimen in AYA.

Deangelo et al #587

AML Therapy

- 1962: 6MP/MTX able to induce temporary remission in few AML pts
- 1970s: Ara-C developed
- Ara-C ± 6TG or DNR – 50% CR
- 1980s
 - 3+7 regimen – Anthracycline (DNR/ADR) + Ara-C – CR rate 65–80%
 - High-dose Ara-C consolidation resulted in long-term survival

Randomized Trials—Conclusions

- Several studies have been done to look at each form of consolidation therapy in first remission AML.
 - Allogeneic transplant
 - Autologous transplant
 - Chemotherapy alone
- No clear winner
- Patients who relapse after chemotherapy can often be salvaged by transplant.
- Trials not designed to determine if BMT may be of benefit in certain populations
 - In young patients who have poor prognostic disease, allogeneic transplant is the treatment of choice if a sibling donor is available.
 - Otherwise chemotherapy or autologous transplant

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Challenges in AML

- Although the majority of adults with AML will respond to induction chemotherapy
 - Certain patients do not respond as well
 - Relapse rates are high
- How can we use the information we have from prognostic factors to make decisions about treatment?

AML Risk Groups

- AML that is less likely to go into remission or more likely to relapse
 - Older patients
 - Patients with secondary disease
 - Unfavorable disease
 - Unfavorable cytogenetics
 - Normal cytogenetics but a mutation in Flt3 AML that is more likely to go into or stay in remission
 - Favorable disease
 - Good cytogenetics
 - Patients with normal cytogenetics but without a mutation in Flt3 and with a mutation in NPM1

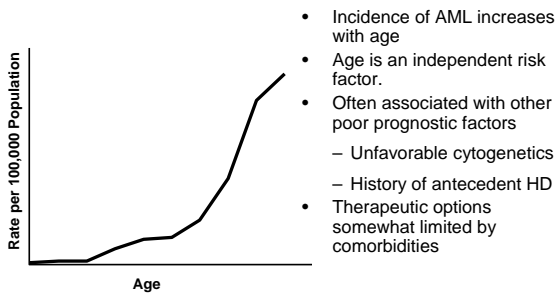
Treatment of Good-Risk AML

- Patients with AML with good-risk cytogenetics (involvement of chromosomes 8,21 or chromosome 16) are more likely to go into remission and more likely to stay in remission
- These patients do particularly well if they are given cycles of Cytarabine in consolidation
- Although we used to think that it didn't matter if the chromosome abnormality is still there after treatment, recent results suggest that there is a threshold amount that matters and that perhaps we can use blood tests after treatment to identify those patients who are more likely to relapse
- More studies are needed to confirm this and to determine if treating these patients earlier will make a difference in their long-term outcome

Treatment Impact on High-Risk AML

- Kienast #169 – Patients with high-risk AML (unfavorable karyotype or Flt3) who respond to induction benefit from allogeneic HSCT as postremission therapy (improved relapse-free survival [RFS] and overall survival [OS])
- Power et al #3491
 - 230 patients with non-M3 AML in CR1 assigned to sibling transplant if available
 - Patient with Flt3 ITD who get chemo do worse, but those who get transplant do just as well as Flt3 ITD negative patients.
- Kienast et al #328 – Patients with extremely favorable Flt3 profile do even better with transplant than other patients—so should they be transplanted also?

Elderly AML



MDR and Elderly AML

- The MDR gene results in a lower rate of remission because the cells "pump out" the chemotherapy
- MDR-1/P-gp expression is more common when patients have relapsed AML but it increases with age and is found in the majority of elderly patients with AML
- Trials of old agents that block MDR also blocked the drug from treating the leukemia
- Zosuquidar is a potent and specific p-gp inhibitor
 - Study of 72 hour infusion with chemotherapy recently reported
 - Zosuquidar well tolerated
 - Benefit appears most significant in elderly secondary AML
 - Phase III trial planned

Leith et al, Blood 1997.

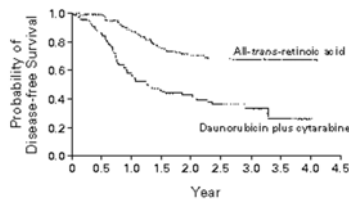
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APL and ATRA

- t(15;17) determined in the 1970s.
 - 1990s: it was determined that the t(15;17) resulted in an abnormal gene.
 - This abnormal gene was found to affect the way the cells handled a chemical in the body called retinoic acid that allowed the cells to mature properly.
 - In the presence of the abnormal gene, the cells were not able to mature properly.
- Through a sequence of clinical trials, it was determined that by simply giving a vitamin A derivative, ATRA, in addition to chemotherapy, we are able to overcome the problem.
 - More patients go into remission
 - More patients stay in remission

APL Is Now One of the Most Curable Forms of Leukemia



	1ST YR	2ND YR	3RD YR	4TH YR	5TH YR
	no. of events/no. at risk				
Daunorubicin plus cytarabine	49/220	14/61	6/35	1/8	0/0
All-trans-retinoic acid	15/224	18/98	2/67	0/21	1/8

Tallman, MS et al. *N Engl J Med.* 1997;337:1021-1028



APL Today

- Newest studies show a role for arsenic trioxide
- Agent recommended for treatment of relapsed disease
- Randomized trials now show a benefit in patients in first complete remission

	-ATO	+ATO
WBC <10k	70	89
WBC >10k	52	86

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New Approaches in AML

- | | |
|--|--|
| <ul style="list-style-type: none"> • Farnesyltransferase inhibition <ul style="list-style-type: none"> - Tipifarnib - SCH66336 • FLT3 inhibition <ul style="list-style-type: none"> - Tandutinib (MLN518) - PKC412 - Lestaurtinib (CEP701) • Drug-resistance modulation <ul style="list-style-type: none"> - Zosuquidar - PSC-833 | <ul style="list-style-type: none"> • HDAC inhibition <ul style="list-style-type: none"> - Vorinostat - MGCD0103 • Others <ul style="list-style-type: none"> - Clofarabine - Decitabine - Azacitidine - Cloretazine (VNP40101M) |
|--|--|

Conclusions

- Treatment of acute leukemia results in significant remissions and long-term disease-free survival.
- Clinical trials have allowed us to learn more about the different types of leukemia and to evaluate new therapeutic options and develop improved regimens.
- Patients with normal cytogenetics may still have molecular findings that can affect the disease biology or prognosis.
- Newer therapies will hopefully further improve remission rates and decrease toxicities.
