ACUTE MYELOID LEUKEMIA: DIAGNOSIS, TREATMENT, AND EXPERIMENTAL THERAPIES

Arthur E. Frankel, MD

8/4/06
PATIENT MH

HPI: 72YO HAWAIIAN FEMALE WITH ONE WEEK OF FATIGUE. SHE DENIES FEVERS, BLEEDING, MASSES.


ILLNESSES ARE HTN, DM, HYPERCHOLESTEROLEMIA, PERIUMBILICAL HERNIA.

ALLERGY TO KEFLEX; HABITS-NO SMOKING/NO ETOH.

FH: MOTHER DIED 75YO BREAST CA. FATHER DIED HT AND CAD.

SH: RETIRED. LIVES WITH FAMILY IN KILLEEN.

ROS: CBC ONE MONTH AGO HAD HGB 10.
PATIENT MH

PE: AFEBRILE BP140/70 P90 R12 WGT180#

SKIN-NO PETECHIAE OR ECCHYMOSES
HEENT-OP CLEAR WITH NO ULCERATIONS
NECK-SUPPLE AND NO ADENOPATHY
CHEST-CLEAR TO P&A
COR-RRR AND NO M/G/R
ABDOMEN-LARGE PERIUMBILICAL HERNIA
LEGS-NO C,C,E
NEURO-MOTOR/SEN/COORD/REFLEX/MS NORMAL

LAB: WBC 51,700 WITH 75% BLASTS
HGB 5.6, HEMATOCRIT 18, RETIC 0.4%
PLAT 36,000
CREATININE 1.6, NA 131, BUN 36
LFTS, FOLATE, IRON, B12-NORMAL
CT CHEST AND ABDOMEN-NEG
PERIPHERAL SMEAR MH
HOW DO WE APPROACH THIS PATIENT?

ACUTE ISSUES
DIAGNOSIS
STAGING
PROGNOSIS/THERAPY
SUPPORTIVE CARE
EXPERIMENTAL THERAPY
BONE MARROW MH
BLAST CHARACTERIZATION MH

CD13, 34, HLA-DR POSITIVE; CYTOGENETICS--HYPERDIPLOID
BLAST CYTOGENETICS MH

HYPERDIPLOID CHROMOSOMES
DX: ACUTE MYELOID LEUKEMIA (NOT APL)

TX: CENTRAL LINE, ECHO, FREQUENT CBC, CMP, DIC, 7+3 CHEMOTHERAPY, HSV ASSAY, CULTURE/ANTIBIOTICS FOR FEVERS, ANTIEMETICS, TRANSFUSIONS, FOLLOWUP DAY 15 BONE MARROW BX

DAY 15 MARROW SHOWED 10% RESIDUAL BLASTS SO TREATED WITH EXPERIMENTAL AGENT DT\textsubscript{388}IL3 7.07UG/KG TIWEEKLY X2WKS

EVENTS: FEVERS NEEDING ANTIBIOTICS; THROMBOPENIA AND ANEMIA NEEDING TRANSFUSIONS; VLS NEEDING FLUIDS, ALBUMIN AND DIURESIS; SBO FROM HERNIA NEEDING SURGERY; LINE INFECTION NEEDING CATHETER REMOVAL.
HISTORY OF ACUTE MYELOID LEUKEMIA

RUDOLPH VIRCHOW (1821-1902)

DESCRIBED LEUKEMIA, THROMBOSES AND PULMONARY EMBOLISM.

HAJDU, ANN CLIN LAB SCI 35, 203, 2005
AML EPIDEMIOLOGY

12,000 CASES/YEAR IN U.S.
MEDIAN AGE IS 68 YEARS
SIMILAR WORLDWIDE
EQUAL IN MEN/WOMEN & DIFFERENT RACES
4/100,000 PER YEAR
4% OF ALL CANCER DEATHS

GREENLEE, CA CANCER J CLIN 51, 15, 2001; LANDIS, CA J CLIN 48, 6, 1998;
TALLMAN, HEMATOLOGY 81, 143, 2005
## RISK FACTORS FOR AML

<table>
<thead>
<tr>
<th>RISK FACTOR</th>
<th>OR</th>
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<tbody>
<tr>
<td>DOWN’S SYNDROME</td>
<td>50</td>
</tr>
<tr>
<td>FANCONI’S ANEMIA, NF, NOONAN</td>
<td>20</td>
</tr>
<tr>
<td>ORGANOPHOSPHATE FUNGICIDE</td>
<td>11</td>
</tr>
<tr>
<td>ALKYLATING AGENT CHEMOTHERAPY</td>
<td>10</td>
</tr>
<tr>
<td>PREGNANCY DIETARY TOPOII INH. + C609T NQ01</td>
<td>10</td>
</tr>
<tr>
<td>PARENTAL PESTICIDES/PETROLEUM PRODUCTS</td>
<td>5</td>
</tr>
<tr>
<td>COMMERCIAL JET COCKPITS</td>
<td>5</td>
</tr>
<tr>
<td>MATERNAL MARIJUANA</td>
<td>4</td>
</tr>
<tr>
<td>NAGASAKI</td>
<td>3</td>
</tr>
<tr>
<td>BENZENE</td>
<td>3</td>
</tr>
<tr>
<td>MUNITION WORKERS</td>
<td>2</td>
</tr>
<tr>
<td>SMOKERS</td>
<td>2</td>
</tr>
</tbody>
</table>

ORIGIN OF AML IS GENETIC CHANGES IN HEMATOPOIETIC STEM CELL

JORDAN, ONCOGENE 23, 7178, 2004; JORDAN, NAT CLIN PRACT ONCOL 2, 224, 2005
AML GENETIC CHANGES PRODUCE ALTERED GROWTH CONTROL AND DIFFERENTIATION

COMPLEMENTATION GROUP I—PROLIFERATION/SURVIVAL

RAS, KIT, FLT3, NF1, SHP-2 MUTATION
FLT3 ITD

COMPLEMENTATION GROUP II—DIFFERENTIATION/SELF-RENEWAL

RUNX1-ETO, CBFBETA-SMMHC, PML-RARALPHA, GATA-1 MUTATION, OTT-MAL, MLL FUSIONS

GILLILAND, HEMATOLOGY 80, 2004
AML SYMPTOMS

- OVER DAYS-WEEKS RATHER THAN MONTHS
- LETHARGY, WEAKNESS, PALLOR, DIZZINESS, TROUBLE STANDING OR WALKING, HEADACHE
- EASY BRUIISING, UNUSUAL BLEEDING, FREQUENT NOSE BLEEDS, BLEEDING GUMS, PETECHIAE
- REPEATED, FREQUENT INFECTIONS, FEVER THAT LASTS FOR SEVERAL DAYS
- BACK, LEG AND JOINT PAIN
AML SIGNS

- PALLOR
- ECCHYMOSES, PETECHIAE, FUNDAL HEMORRHAGE
- ADENOPATHY, HEPATOSPLENOMEGALY
- GUM OR SKIN INFILTRATION
AML PALLOR, PETECHIAE, AND CELLULITIS

PALLOR

PETECHIAE

CELLULITIS
AML GUM AND SKIN INFILTRATION

GUM

SKIN
# AML Laboratory Abnormalities

<table>
<thead>
<tr>
<th>CBC</th>
<th>LOW HGB, LOW OR HIGH WBC, PLATELETS, CIRCULATING BLASTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>COAGS</td>
<td>LOW FIBRINOGEN, HIGH PT, HIGH PTT, HIGH D-DIMER</td>
</tr>
<tr>
<td>CHEMISTRIES</td>
<td>HIGH CR, UA, PHOSPHORUS</td>
</tr>
</tbody>
</table>
PANCYTOPENIA DIFFERENTIAL DIAGNOSIS

- LEUKEMIA
- APLASTIC ANEMIA
- MYELODYSPLASIA
- MEGALOBLASTIC ANEMIA (B12 OR FOLATE DEF)
- INFECTION
- AUTOIMMUNE/DRUG REACTION
DIFFERENTIAL DIAGNOSIS—LEUKEMIA

▲ ACUTE MYELOID LEUKEMIA
▲ ACUTE LYMPHOBLASTIC LEUKEMIA
▲ CHRONIC MYELOID LEUKEMIA
▲ CHRONIC LYMPHOID LEUKEMIA
NORMAL BONE MARROW EXAM
AML DIAGNOSIS BY BONE MARROW EXAM

BONE MARROW SHOWS 20% OR MORE MYELOBLASTS, FLOW CYTOMETRY WITH MYELOID MARKERS, CYTOGENETICS CHANGES
ACUTE PROMYELOCYTIC LEUKEMIA (APL)

CHARACTERIZED BY t(15;17), CD13-15-33 POSITIVE AND CD34-DR NEGATIVE, MAY BE CD2 POSITIVE, AUER RODS, DIC, RESPONSIVE TO ATRA/ASO/IDA/MYLOTARG, YOUNGER AGE, MOST WITH LOW WBC, DEATHS MOSTLY IN FIRST WEEKS, MONITOR WITH t(15;17) RT-PCR
SURVIVAL OF PATIENTS WITH NON-M3 AML

BENNET, CANCER 80, 2205, 1997
AML PROGNOSTIC FACTORS

FARAG, BLOOD, EPUB 3/7/06; BALDUS, J CLIN ONCOL 24, 790, 2006; BIENZ, CLIN CAN RES 11, 1416, 2005; DOHNER, J CLIN ONCOL 20, 3254, 2002; STONE, HEMATOL 98, 2004; PAGANO, ANN ONCOL 16, 228, 2005; ANDERSON, BLOOD 100, 3869, 2002; GUPTA, CANCER103, 2082, 2005
THERAPY OF AML

- CONFIRM APL VS OTHER
- STRATIFY BY PROGNOSTIC FACTORS (PS, AGE, CYTO)
- AGGRESSIVE THERAPY, EXPERIMENTAL THERAPY OR SUPPORTIVE CARE

TALLMAN, BLOOD 106, 1154, 2005; BUCHNER, CRIT REV ONCOL HEMATOL 56, 247, 2005
CURRENT S&W DE NOVO AML (NON-APL) THERAPY

<table>
<thead>
<tr>
<th>ASSESSMENT</th>
<th>TREATMENT PLAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS 0-1, &lt;70YO</td>
<td>7+3 AND CONSOLIDATION AND ALLO BMT FOR &lt;50YO AND INT-POOR RISK CYTO</td>
</tr>
<tr>
<td>PS 0-1, &gt;70YO</td>
<td>7+3, MYLOTARG, OR EXPERIMENTAL--DT$_{388}$IL3 OR DECITABINE</td>
</tr>
<tr>
<td>PS 2</td>
<td>SUPPORTIVE CARE</td>
</tr>
</tbody>
</table>

TALLMAN, HEMATOL 2005, 143; TSIMBERIDOU, BR J HAEMATOL 132, 398, 2005; MARCUCCI, CURR OPIN HEMATOL 12, 68, 2005
RELAPSED AML

- 80-90% OF PATIENTS
- SURVIVAL MEDIAN 12 WEEKS
- ALLO BMT IF AVAILABLE
- EXPERIMENTAL THERAPY
<table>
<thead>
<tr>
<th>AGENT</th>
<th>RESPONSE RATE (% CR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZISUQUIDAR-7/3</td>
<td>70</td>
</tr>
<tr>
<td>CLOFARABINE-CYTARABINE</td>
<td>52</td>
</tr>
<tr>
<td>OBLIMERSEN-7/3</td>
<td>48</td>
</tr>
<tr>
<td>REDUCED INTENSITY BMT</td>
<td>36</td>
</tr>
<tr>
<td>BEVACIZUMAB-7/3</td>
<td>33</td>
</tr>
<tr>
<td>FLAVOPIRIDOL-7/3</td>
<td>31</td>
</tr>
<tr>
<td>TROXACITABINE-CYTARABINE</td>
<td>27</td>
</tr>
<tr>
<td>GEMTUZUMAB OZOGAMICIN</td>
<td>17</td>
</tr>
<tr>
<td>TIPIFARNIB</td>
<td>6</td>
</tr>
<tr>
<td>VALPROIC ACID</td>
<td>5</td>
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<tr>
<td>DEPSIPEPTIDE (FK228)</td>
<td>0</td>
</tr>
<tr>
<td>SU11248</td>
<td>0</td>
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<tr>
<td>PKC412</td>
<td>0</td>
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<tr>
<td>CEP701</td>
<td>0</td>
</tr>
<tr>
<td>SU5416</td>
<td>0</td>
</tr>
<tr>
<td>SAHA</td>
<td>ND</td>
</tr>
<tr>
<td>MLN518</td>
<td>ND</td>
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<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50YO/PS0-1/MATCH</td>
<td>CONDITIONING AND ALLO BMT</td>
</tr>
<tr>
<td>&lt;50YO/PS0-1/NO MATCH OR &gt;50YO</td>
<td>DT$_{388}$IL3, MYLOTARG</td>
</tr>
<tr>
<td>PS2</td>
<td>SUPPORTIVE CARE</td>
</tr>
</tbody>
</table>
# AML Supportive Care Issues

<table>
<thead>
<tr>
<th>Complication</th>
<th>Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucositis</td>
<td>Mouthwash, Acyclovir, Antifungal, TPN, Morphine, Palifermin</td>
</tr>
<tr>
<td>Sweet’s Syndrome</td>
<td>Systemic Steroids, Thalidomide</td>
</tr>
<tr>
<td>Tumor Lysis Syndrome</td>
<td>Frequent Blood Tests, Uricase, Allopurinol, Alkaline Hydration</td>
</tr>
<tr>
<td>Line Infection</td>
<td>Cultures, Antibiotics, Change Catheter</td>
</tr>
<tr>
<td>C. Difficile Colitis</td>
<td>CDT Assays, Oral Flagyl or Vancocin</td>
</tr>
<tr>
<td>Aspergillus Pneumonia</td>
<td>Antigen/DNA Assays, CT Scans, Caspofungin, Voriconazole</td>
</tr>
<tr>
<td>Leptomeningeal Leukemia</td>
<td>IT Chemotherapy, Radiotherapy</td>
</tr>
<tr>
<td>Chloromas</td>
<td>Chemotherapy, Radiotherapy</td>
</tr>
<tr>
<td>Bleeding Diathesis—Non-DIC</td>
<td>Blood Products, Amicar</td>
</tr>
<tr>
<td>Fluid Overload/Heart Failure</td>
<td>Diuretics, ACE Inhibitor</td>
</tr>
</tbody>
</table>

TARGETED THERAPIES OF LEUKEMIC STEM CELLS

GUZMAN, CANCER CONTROL 11, 97, 2004
CELL SURFACE MARKER ON LEUKEMIC STEM CELLS

TESTA, LEUKEMIA 18, 219, 2004; JORDAN, ONCOGENE 23, 7178, 2004;
DT$_{388}$IL3 MOLECULE

TRANSLOCATION

IL3

CATALYTIC

FRANKEL, PROT ENG 13, 575, 2000; URIETO, PROT EXP PURIF 33, 123, 2004
MECHANISM OF ACTION OF DT$_{388}$IL3

AML STEM CELL → IL3R → DT$_{388}$IL3 → ENDOSONME → DTA → EF2

FRANKEL, LEUK 14, 576, 2000; ALEXANDER, BIOCONJ CHEM 11, 564, 2000;
ALEXANDER, LEUK RES 25, 875, 2001; FEURING-BUSKE, CANCER RES 62, 1730, 2002;
BLACK, LEUKEMIA 17, 155, 2003; COHEN, LEUK & LYMPH 45, 1647, 2004; COHEN,
CANCER IMMUNOL IMMUNOTHER 54, 799, 2005
PHASE I CLINICAL TRIAL OF $\text{DT}_{388}\text{IL3}$ FOR REFRACTORY OR POOR-RISK AML

Inter-patient dose escalation 4, 5, 7, 9 ug/kg days M-W-F x 2 weeks over 15 minutes IV infusion and prophylaxis with NS IV acetaminophen, diphenhydramine, vitamin K, moxifloxacin, fluconazole, hydrocortisone, prn meperidine/lorazepam/promethazine given inpatient.

Monitor histories, exams, blood counts, chemistries, urinanalysis, coagulation studies, Bone marrows.

Measure protein levels, antibody levels, blast IL3R.
SUBJECT CHARACTERISTICS (27 TOTAL)

MEDIAN AGE: 59 YRS (25 - 81)

SEX: 13 MALES, 14 FEMALES

RELAPSE: 2 DE NOVO, 10 FIRST, 7 SECOND, 8 REFRACTORY

TRANSPLANT: 1 AUTO, 1 ALLO, 25 NONE

CYTOGENETICS: 10 UNFAVORABLE, 16 INTERM., 1 NOT DONE

PRIOR MDS/ THERAPY RELATED: 3 MDS, 1 THERAPY RELATED, 23 ABSENT
DT388 IL3 GR 2 TOXICITIES*

*SEVEN PTS TREATED AT 4µG/KG; EIGHT PTS TREATED AT 5.3µG/KG; ELEVEN PTS TREATED AT 7.1µG/KG; ONE PT TREATED AT 9µG/KG
<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Pre-infusion blast %</th>
<th>Overall Response</th>
<th>Length of response (mos)</th>
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</thead>
<tbody>
<tr>
<td>9</td>
<td>50%</td>
<td>PR</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>69%</td>
<td>MR with 93% reduction</td>
<td>2</td>
</tr>
<tr>
<td>14</td>
<td>90%</td>
<td>MR with 89% reduction</td>
<td>1</td>
</tr>
<tr>
<td>15</td>
<td>80%</td>
<td>MR with 90% reduction</td>
<td>1</td>
</tr>
<tr>
<td>19</td>
<td>30%</td>
<td>CR</td>
<td>ongoing for &gt;7</td>
</tr>
<tr>
<td>23</td>
<td>39%</td>
<td>PR</td>
<td>3</td>
</tr>
</tbody>
</table>
DT$_{388}$IL3 AML #19 RESPONSE

PRE

POST 3 MOS

ANC

PLAT
FUTURE WORK

- FINISH PHASE I $\text{DT}_{388}$IL3
- EXPAND PHASE II WITH MEASUREMENTS IL3R
- PREPARE $\text{DT}_{388}K116W$ FOR CLINICAL STUDY

YALCINTEPE, BLOOD, IN PRESS; HOGGE, CLIN CANCER RES 12, 1284, 2006; TESTA, BLOOD 106, 2527, 2005; HOGGE, LEUK RES 28, 1221, 2004; LIU, EXP HEMATOL 32, 277, 2004
CONCLUSIONS

AML IS AN ACUTE TO SUBACUTE ILLNESS USUALLY WITH ABNORMAL CBC

DIAGNOSIS REQUIRES BONE MARROW ASPIRATE/BIOPSY

FACTORS INCLUDING PERFORMANCE STATUS, AGE, AND CYTOGENETICS AFFECTS TREATMENT AND PROGNOSIS

STANDARD THERAPY IS 7+3 WITH CONSOLIDATION

RELAPSE HAS POOR SURVIVAL AND IS TREATED WITH TRANSPLANT OR EXPERIMENTAL THERAPY

SUPPORTIVE CARE IS COMPLEX
SCOTT & WHITE CRI RESEARCH TEAM

CAROL CARTER, RALPH ABI-HABIB, JUNG-HEE WOO, JANELLE ORTIZ, TONY DANG, YUNPENG SU, JEN-SING LIU, JEFFREY BROWNING, ARTHUR FRANKEL, RAVIBHUSHAN SINGH, LORIE FARES, MONICA WEIR, RANDALL ALFANO, MADAN KATRAGADDI, JOHN STRAWSER, SOO KANG, COURTNEY IRELAND, NICOLLE STRAUSS, NANCY BOWMAN, JEFFREY PERKINS.

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