The Big Sort: Successful Use of Leukocytapheresis in a Patient with a Mature B-cell Neoplasm and Leukostasis

Colin Godwin, M.D.

Discussant: Laura Connelly-Smith, MBBCh, DM

Hematology Fellow’s Conference 2/19/16
A phone call from Eastern Washington...

• “We have a 64 year-old woman here with a WBC count of 600,000.”
• “Our pathologist is telling us that there are 93% myeloid blasts on the smear.”
• “She looks fine.”
Hyperleukocytosis

• Typically defined as WBC or leukemic blast count >100,000/ul.
• The usual suspects: AML, ALL, CML, and CLL
• Complicates approximately 10-30% of ALL and 5-13% of adult AML cases.

<table>
<thead>
<tr>
<th>TABLE I Factors associated with hyperleukocytosis in AML and ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AML</strong></td>
</tr>
<tr>
<td>Age &lt; 1 year</td>
</tr>
<tr>
<td>FAB M4, M5</td>
</tr>
<tr>
<td>APL microgranular variant (M3v)</td>
</tr>
<tr>
<td>11q23 rearrangements</td>
</tr>
<tr>
<td>inv(16)(p13q22)</td>
</tr>
<tr>
<td>Chromosome 6 abnormalities</td>
</tr>
<tr>
<td>Expression of lung resistance protein (LRP)</td>
</tr>
<tr>
<td>+FLT3-ITD</td>
</tr>
</tbody>
</table>

Hyperleukocytosis

• Associated with increased risk of early mortality in AML, often 5-30%.
• Unclear if associated with lower remission rates in AML.
• Likely does not have a similar impact on early death in ALL unless WBC > 250,000/μl.
• Overall poor prognosis when WBC count > 30,000/μl in B-ALL and > 100,000/μl in T-ALL.
• In one analysis of CLL patients, 2.7% had WBC > 150,000/μl, none with significant complications and WBC not independently associated with poorer prognosis.
• Complicates approximately 12% of CML cases.
• Associated with higher rates of complications: TLS, DIC, leukostasis.
A rapid flight later, and another phone call...

• “Colin, the patient is here and she doesn’t look so good.”

• “She’s somnolent and has difficulty answering questions.”

• “She’s tachypneic. She’s satting 93% on a 10L oximizer.”
Physical exam

- **VS:** T 36.5, HR 102, RR 30, BP 133/77, 93% on 10 L oximeter
- **General:** lying in bed, minimally responsive to questions
- **HEENT:** normocephalic, atraumatic
- **Lymph:** no significant cervical, supraclavicular, axillar or inguinal lymphadenopathy
- **Pulmonary:** crackles in bases bilaterally
- **Cardiovascular:** tachycardic, no murmurs
- **Abdomen:** non-tender, palpable spleen
- **Extremities:** trace edema bilaterally
- **Neuro:** oriented to self, daughter's name, hospital but otherwise with delayed response to questions. Able to follow some commands without lateralizing deficits.
Initial lab testing

- WBC 614.40, Hct 31, Plt 9
- Na 125, K >10.0, Cr 2.09
- Uric acid 20.9, LDH 7446
- D-dimer >40, PT 16, PTT 22, fibrinogen 389
Images courtesy of Dr. Kerstin Edlefsen, Hematopathology.
Normal smear

Albumin smear

Images courtesy of Dr. Kerstin Edlefsen, Hematopathology.
Leukostasis: clinical characteristics

• A syndrome caused by end-organ complications of microvascular leukoaggregates, hyperviscosity, tissue ischemia, infarction and hemorrhage.
• Characterized most frequently by pulmonary and CNS manifestations.
• Early mortality can be up to 70% in patients with respiratory distress or neurologic symptoms.
• Can be difficult to identify clinically since there can be other explanations for symptoms in the setting of acute leukemia.
Leukostasis: clinical characteristics

<table>
<thead>
<tr>
<th>Organ</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>Dyspnea, hypoxemia, diffuse alveolar hemorrhage, respiratory failure</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>Confusion, somnolence, dizziness, headache, delirium, coma, focal neurologic deficits</td>
</tr>
<tr>
<td>Eye</td>
<td>Impaired vision, retinal hemorrhage</td>
</tr>
<tr>
<td>Ear</td>
<td>Tinnitus</td>
</tr>
<tr>
<td>Heart</td>
<td>Myocardial ischemia/infarction</td>
</tr>
<tr>
<td>Vascular system</td>
<td>Limb ischemia, renal vein thrombosis, priapism</td>
</tr>
</tbody>
</table>

Reproduced from Röllig and Ehninger, 2014.
# Leukostasis: clinical characteristics

<table>
<thead>
<tr>
<th>Group</th>
<th>Probability of leukostasis syndrome</th>
<th>Severity of symptoms</th>
<th>Pulmonary symptoms</th>
<th>Neurologic symptoms</th>
<th>Other organ systems</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Not present</td>
<td>No limitations</td>
<td>No symptoms and no limitations in ordinary activities</td>
<td>No neurologic symptoms</td>
<td>No symptoms</td>
</tr>
<tr>
<td>1</td>
<td>Possible</td>
<td>Slight limitations</td>
<td>Mild symptoms and slight limitation during ordinary activity, comfortable at rest</td>
<td>Mild tinnitus, headache, dizziness</td>
<td>Moderate fatigue</td>
</tr>
<tr>
<td>2</td>
<td>Probable</td>
<td>Marked limitations</td>
<td>Marked limitation in activity because of symptoms, even during less than ordinary activity, comfortable only at rest</td>
<td>Slight visual disturbances(^1), severe tinnitus, headache, dizziness</td>
<td>Severe fatigue</td>
</tr>
<tr>
<td>3</td>
<td>Highly probable</td>
<td>Severe limitations</td>
<td>Dyspnoea at rest, oxygen or respirator required</td>
<td>Severe visual disturbances(^1) (acute inability to read), confusion, delirium, somnolence, intracranial haemorrhage</td>
<td>Myocardial infarction, priapism, ischaemic necrosis</td>
</tr>
</tbody>
</table>

\(^1\)Blurred vision, diplopia, hemianopia.
Leukostasis: mechanisms

- Rheology – The study of the flow of matter.

Leukostasis: mechanisms

- Cytoadhesive properties

Reproduced from Rollig and Ehninger.
Leukostasis: disease-specific risk factors

- Most commonly seen in AML, and can occur even in WBC >50K in patients with monocytic lineage AML, but can occur relatively frequently in AML with WBC > 100K.

- Rare for ALL to have leukostasis unless WBC >400K.

- Occurs at the case report level for patients with CLL, CMML.

- Can be associated with priapism in CML patients with WBC >500K.
So what do we do tonight?

- Treat the tumor lysis syndrome: fluids, allopurinol, rasburicase.
- Supplemental oxygen.
- Avoid transfusions where possible.
- **Urgent leukoreduction.**
So what do we do tonight?

- Leukocytapheresis
- No leukocytapheresis
Leukocytapheresis (LCP)
LCP: practical considerations and complications

• Need either two large bore (16-18 gauge) peripheral IVs or a large bore central venous catheter.

• Minimum platelet count of 20,000/ul required given loss during procedure.

• Can be complicated by hypocalcemia because of citrate in circuit.
LCP: the data

• No randomized clinical trials; majority are retrospective analyses in AML.
• All studies have shown rapid lowering of WBC count, up to 30-60% with a single cycle.
• Differing institutional standards of implementation.
• Possible decrease in early mortality in some studies, not in others.
• Generally no improvement in overall survival with use of LCP.
• One study showing a trend toward increase in mortality in LCP group.
Leukapheresis and low-dose chemotherapy do not reduce early mortality in acute myeloid leukemia hyperleukocytosis: A systematic review and meta-analysis

Sapna Oberoi\textsuperscript{a}, Thomas Lehrnbecher\textsuperscript{b}, Bob Phillips\textsuperscript{c,d}, Johann Hitzler\textsuperscript{a}, Marie-Chantal Ethier\textsuperscript{e}, Joseph Beyene\textsuperscript{e,f}, Lillian Sung\textsuperscript{a,e,*}

\textsuperscript{a} Division of Haematology/Oncology, The Hospital for Sick Children, Toronto, Canada
\textsuperscript{b} Pediatric Hematology and Oncology, Johann Wolfgang Goethe University, Frankfurt, Germany
\textsuperscript{c} Leeds General Infirmary, Leeds Teaching Hospitals, NHS Trust, Leeds, UK
\textsuperscript{d} Centre for Reviews and Dissemination, University of York, York, UK
\textsuperscript{e} Program in Child Health Evaluative Sciences, The Hospital for Sick Children, Toronto, Canada
\textsuperscript{f} Department of Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, Canada

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Leukapheresis</th>
<th>No Leukapheresis</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bug 2007</td>
<td>4 events, 25 total</td>
<td>9 events, 28 total</td>
<td>0.40 [0.11, 1.52]</td>
</tr>
<tr>
<td>Chang 2007</td>
<td>12 events, 28 total</td>
<td>13 events, 47 total</td>
<td>1.96 [0.73, 5.25]</td>
</tr>
<tr>
<td>Giles 2001</td>
<td>9 events, 71 total</td>
<td>17 events, 75 total</td>
<td>0.50 [0.20, 1.20]</td>
</tr>
<tr>
<td>Inaba 2008</td>
<td>1 event, 36 total</td>
<td>16 events, 70 total</td>
<td>0.10 [0.01, 0.76]</td>
</tr>
<tr>
<td>Sung 2012</td>
<td>1 event, 16 total</td>
<td>3 events, 73 total</td>
<td>1.56 [0.15, 16.00]</td>
</tr>
<tr>
<td>Ventura 1988</td>
<td>7 events, 61 total</td>
<td>10 events, 24 total</td>
<td>0.18 [0.06, 0.56]</td>
</tr>
</tbody>
</table>

Total events: 34 (Leukapheresis) vs 68 (No Leukapheresis)

Heterogeneity: $\tau^2 = 0.74$; $\chi^2 = 13.94$, df = 5 ($P = 0.02$); $I^2 = 64\%$
So what do we do tonight?

Supported by AFSA guidelines

- Already in spontaneous tumor lysis
- Temporize for further diagnostic work-up
- Speed of effect
- Leukocytapheresis

Only temporary
No clear evidence
Thrombocytopenia
Need for access
No leukocytapheresis
So what do we do tonight?

Supported by AFSA guidelines

Already in spontaneous tumor lysis

Temporize for further diagnostic work-up

Speed of effect

Leukocytapheresis

Only temporary

No clear evidence

Thrombocytopenia

Need for access

No leukocytapheresis
Hospital course

• Patient transfused platelets and CVC placed for urgent leukocytapheresis.
• Underwent 3 x total blood volume leukocytapheresis runs with improvement in WBC to 300.
• Improvement in mentation and oxygenation.
A diagnostic result...

**INTERPRETATION**
Peripheral blood: Abnormal, mature B-cell population identified (see comment).

**COMMENT**
Flow cytometry reveals an abnormal mature B-cell population having aberrant expression of CD38 (slightly increased), FMC-7, and lambda light chain restriction with normal expression of CD19, CD20, and CD45 without CD5, CD10, CD23, CD123, CD200, or ZAP-70. Additional evaluation shows the abnormal B-cell does not have expression of TdT or CD34, consistent with a mature B-cell process. The abnormal population represents 91% of the total white cells. This immunophenotype and the clinical presentation of this non-Hodgkin, mature B-cell lymphoma is not specific for diagnostic classification.

The absence of CD5 co-expression argues against typical variants of CLL/SLL and mantle cell lymphoma, both of which are usually CD5+ positive. The absence of CD10 expression argues against typical follicular lymphoma and Burkitt lymphoma. As the abnormal B-cell population has expression of FMC-7 without CD23 or CD200, classification as an atypical CD5-negative mantle cell lymphoma may be considered. Accordingly, FISH/cytogenetic evaluation for the t(11;14) **CCND1/IGH** translocation is strongly advised (Liu 2002). Additionally, as this may alternately represent an atypical double-hit lymphoma, FISH for t(14;18) **BCL2-IGH**, **MYC**, and **BCL6** should be also be performed and excluded. Lastly, other diagnostic consideration may include B-cell prolymphocytic leukemia, large B-cell lymphoma, or marginal zone lymphoma. Careful clinical, cytogenetic, and morphologic correlation will be required for definitive classification. Sampling of disease-involved lymph node or tissue could provide histologic material to aide in classification.

No immunophenotypic evidence of a myeloid stem cell disorder (e.g. myelodysplastic syndrome or myeloproliferative neoplasm) or T cell non-Hodgkin’s lymphoma is identified. However, a low-grade stem cell disorder cannot be entirely excluded and clinical, cytogenetic, and morphologic correlation is required.

Would mantle cell lymphoma be a surprise?

Case report: mantle cell lymphoma, prolymphocytoid variant, with leukostasis syndrome

Marc D Smith¹, Timothy P Singleton¹, Savitha Balaraman², Ishmael Jaiyesimi², Barbara O’Malley¹, Abdul Al-Saadi³ and Joan C Mattson¹

¹Department of Clinical Pathology; ²Department of Hematology/Oncology and ³Department of Anatomic Pathology, William Beaumont Hospital, Royal Oak, MI, USA

Case Report

Therapeutic Leukocytapheresis for Improvement in Respiratory Function in a Woman With Hyperleukocytosis and Mantle Cell Lymphoma With a Circulating Small Lymphocyte Phenotype

Laura Kwan,¹,⁵,⁷ Jeanne Linden,¹,⁷ Kathleen Gaffney,¹,⁷ Mindy Greene,¹,⁷ Michelle Vauthrin,¹,⁷ Muthalagu Ramanathan,¹,⁴,⁵,⁷ and Robert Weinstein¹,²,⁴,⁵,⁶,⁷,⁸

Rapid Treatment of Leukostasis in Leukemic Mantle Cell Lymphoma using Therapeutic Leukapheresis: A Case Report

Xuan Duc Nguyen¹,*, Paul La Rosée², Thomas Nebe³, Harald Klüter¹, and Dieter Buchheidt²
**Clinical Indication:** Lymphoma

**Previous Tests:**
NF15-1034 12/30/2015  nuc ish(MYCx2)(5'MYC sep 3'MYCx1)[183/200], (CCND1x2, IGHX3~4)[192/200], (IGHx3~4, BCL2x2)[193/200]
NF15-1039 12/31/2015  nuc ish(MYCx3, CEP8x2, IGHX3~4)(MYC con IGHX2)[140/200], (IGHx2)(5'IGH sep 3'IGHx1)[29/200]/(IGHx2)(5'IGH sep 3'IGHx2)[159/200]

**ISCN Diagnosis:**
46,XX,dup(1)(q21q43), del(6)(q21q26), t(8;14)(q24.2;q32), del(9)(p13), del(12)(q22q24.1), add(14)(q32), add(18)(p11.3)[13]/46,XX[6]

**Summary:** COMPLEX female karyotype with t(8;14) and gain of 1q

**Diagnosis and Comments:** G-banded chromosome analysis revealed a complex female karyotype with multiple structural abnormalities in 13 of 20 cells examined, including a duplication of part of 1q, deletions of 6q, 9p and 12q, a translocation t(8;14), and additional materials of unknown origins attached onto 14q32 and 18p11.3 resulting in unclear net imbalance. These findings are consistent with the FISH analysis of the same specimen (NF15-1034 and NF15-1039). MYC rearrangement is common in non-Hodgkin lymphomas (NHL), especially in the Burkitt lymphoma, and associated with poor prognosis and aggressive behavior.
Final diagnosis

Aggressive mature B-cell neoplasm with myc translocation.
Hospital course

• Patient started on modified hyperCVAD cycle 1B with cytarabine 1 g/m² and dexamethasone.
• Initial worsening of tumor lysis syndrome and hemodynamic status, but then recovered.
• Further improvement in respiratory status and mentation, transferred out of ICU.
• Once cytopenic, given initial dose of rituximab and discharged.
• Later started on R-EPOCH as definitive therapy with CNS prophylaxis.
WBC

Leukocytapheresis x 3 TBV
Cyatarabine 1 g/m²
Dexamethasone 40 mg
Conclusions

• Though most common in acute leukemias, hyperleukocytosis and leukostasis can complicate other neoplasms with high circulating WBC.
• There are no randomized data to support the routine use of LCP.
• LCP can be safe and effective in patients with leukostasis while additional stabilizing and diagnostic interventions are performed.
• Though leukostasis in mature B-cell neoplasms is exceedingly rare, in this case LCP was a safe and effective treatment.
Acknowledgements

* Janis Abkowitz
* Laura Connelly-Smith
* Michael Linenberger
* Billy Chen
* Sheida Aalami
* Sam Rayner
* Guang-Shing Chen
* Samatra Doyle
* Ryan Cassaday
* Kerstin Edlefsen
References


