RISK STRATIFICATION IN A PATIENT WITH INV 16 AML.

PRESENTED BY EDMOND MARZBANI
FACULTY DISCUSSANT: DR. ESTEY
Overview

1. Case presentation.

2. Treatment related myeloid neoplasms.

3. Core binding factor AML.

4. KIT mutation and risk stratification.

5. Dr. Estey.
HPI

- 54 year old woman with a history of breast cancer s/p treatment in 2009 who was at baseline level of health until 10/2010 when she developed progressive fatigue, dyspnea, and easy bruising.

- CBC revealed an initial WBC of 50K (30% blasts), HCT of 15 (MCV 101), and PLT 37K.

- Marrow revealed at least 50% blasts which were MPO positive. She was immediately flown to UWMC from AK.
1. Stage III C hormone-positive HER-2 negative invasive ductal carcinoma.

- She was diagnosed with clinical stage T3, N2, ER/PR+, HER-2/NEU-breast cancer.
- She received neoadjuvant AC for 15 weeks with an adriamycin dose of 24 mg/m2 weekly for cumulative exposure 360 mg/m2.
- She received paclitaxel for 12 weeks with clinical and radiographic improvement.
- Mastectomy was performed 6/2009 with residual T1c, N3 (18+ nodes with extracapsular extension).
- Radiation therapy with 5540 cGy to the right chest wall and 4500 cGy to the axillary fields. Highest risk volume was 6040 cGy.

1. Performance status = 1.
Physical examination was unremarkable with exception of significant, diffuse bruising.

Electrolytes, chemistry panel, LFTs were normal.

CBC: 47.85, HCT 31 (MCV 92), PLT 47.
  - Differential: N770, L9810, M18810, E380, B380, UC 17660

COAGS: PT 16.0, INR 1.3, PTT 38, Fibrinogen 421, D-dimer 0.23.
Flow cytometry

- INTERPRETATION
  - Bone marrow, aspirate: Acute myeloid leukemia (see comment).
Therapy-related myeloid neoplasms (T-MN)

- Approximately 10-15% of myeloid neoplasms arise after chemotherapeutic treatment and/or radiation for a primary malignancy.

- Incidence of T-MN thought to be less than 1% with cytotoxic therapy/radiation but depends on dose and agents involved.

- Generally thought to do poor compared to de novo AML.
# Cytotoxic agents implicated

<table>
<thead>
<tr>
<th>Agent type</th>
<th>Agent</th>
<th>Prognosis</th>
<th>Latency</th>
<th>Preleukemic Phase</th>
<th>Cytogenetic abnormalities</th>
<th>FAB Class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylators</td>
<td>Melphalan, Cyclophosphamide</td>
<td>Poor</td>
<td>Long</td>
<td>Yes</td>
<td>Chromosomes 5 and 7</td>
<td>M1/2 or M6/7</td>
</tr>
<tr>
<td>Topoisomerase II inhibitor</td>
<td>Anthracyclines, anthracenediones, epipodophyllotoxins</td>
<td>Better</td>
<td>Short</td>
<td>No</td>
<td>11q23</td>
<td>M4/5</td>
</tr>
<tr>
<td>Taxanes</td>
<td>Paclitaxel, Docetaxel</td>
<td>Good</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Chromosome 16 (p13q22)</td>
<td>M4E0</td>
</tr>
</tbody>
</table>
Aberrant karyotypes were detected in 86% of t-AML and 57.6% of de novo AML.

Favorable, intermediate, and unfavorable cytogenetics were seen in 25.8, 28.0, and 46.2% of T-AML and in 22.2, 57.3, and 20.4% of de novo AML.

Favorable karyotypes equivalent but less intermediate and more unfavorable in the T-AML group compared to de novo.

T-AML portends a poor prognosis.

Median OS of the de novo AML was 15 months while it was only 10 months in t-AML.

Complete remission rates were significantly lower in T-AML in those with intermediate and unfavorable karyotype but not with favorable cytogenetics.

No differences in the relapse rate were observed between T-AML and de novo AML except in favorable group, where rate was 3x in T-AML compared to de novo.
If you were asked what her expected cytogenetic abnormality would be by your attending, you would answer:

11q23.

ISCN Diagnosis:
46,XX,inv(16)(p13.1q22)[17]/46,XX[3].

Summary: POSITIVE for inv(16).
Core binding factor AML

- Cytogenetic abnormalities inv(16) and t(8;21) disrupt genes encoding subunits of core binding factor.
  - Heterodimeric transcription factor involved in regulation of hematopoiesis.
  - AML subgroups with inv(16) and t(8;21) are collectively referred to as CBF AML.

- Both translocations produce dominant negative inhibitors of normal myeloid differentiation.
In addition to sharing a similar pathogenetic mechanism:

- Prognosis is considered favorable compared to other forms of adult AML.
- Higher sensitivity to high dose cytarabine.
Inversion (16)

- Abnormalities of chromosome 16 are seen in 7% of adults with de novo AML.

  - Broadly, two groups are defined including AML with inv(16)(p13.1;q22) or t(16;16)(p13.1;q22) and AML with other abnormalities of chromosome 16.

  - Distinction is made because the former two have a favorable prognosis with standard therapy while those with other abnormalities do not.

  - This cytogenetic abnormality is diagnostic of AML regardless of the blast count.
AML with inv(16) typically demonstrates monocytic and granulocytic differentiation with abnormal eosinophils in the bone marrow.

Given that this patient had inv(16), Delauney et al. paper examined to evaluate prognosis in de novo inv(16) AML.

- Outcome and prognostic factors for complete remission, disease free survival, overall survival of patients in complete remission were evaluated in 110 patients.

- Total of 102 patients (93%) reached CR without difference among trials.
  - 6 died during induction, typically from TLS and coagulopathy.

- Overall, 3 year survival estimate was 58% and 3 year DFS was 48%

- At 3 years, cumulative incidence of relapse was 42% and cumulative incidence of death was 10%.
Univariate analysis revealed age was not a bad-prognosis factor for CR. Higher WBC predicted induction failure, as did lower platelet count.

Presence of other additional chromosome structure or number abnormalities did not affect CR rate.

Advanced age did worsen DFS in CR patients.

Given this, do inv(16) T-AML patients do worse than de novo inv(16)?
Do patients with TAML/inv(16) do worse than de novo inv(16)?

- Overall survival by matched analysis (age, PS, additional cytogenetic abnormality). Patients had a worse OS (p=0.001) and EFS (P=0.003) with matched treatment-related CBF (inv16 and t(8;21)) AML patients compared with de novo disease. Borthakur et al. Cancer 2009;115:3217-21.

- Schoch et al. found similar result when evaluating OS and relapse in “favorable” cytogenetic population (t(8;21), inv(16), t(15;17) comparing T-AML and de novo.

- In subgroup analysis, true for t(8;21) but not for inv(16).

- In inv(16), median OS was neither reached in the T-AML, nor in the de novo AML group with OS rate at 5 years being 61.5% in T-AML compared to 77.8% in de novo AML (P=0.33).
Do patients with TAML/inv(16) do worse than de novo inv(16)?

- Although data is limited, treatment related inversion(16) seems to have a comparable outcome with de novo inversion(16). Not true for other CBF AMLs.

- Age, however, predicts a higher relapse rate.

- How can one further risk stratify inversion(16)?
Further risk stratification: muKIT

- “Good” prognosis CBF AML still has 50% OS at 5 years, suggesting that some have a more aggressive leukemia particularly prone to relapse.

- KIT status is considered a candidate for risk stratification.
  - KIT is a 145 kD transmembrane glycoprotein located at 4q11-12.
  - Member of type III receptor tyrosine kinase family that is involved in downstream signaling pathways involved in proliferation, differentiation, and survival.
  - Ligand independent activation can be caused by gain-of-function mutations seen in CBF AML.
  - KIT mutations preferentially associated with CBF AML.
Paschka et al. Adverse Prognostic Significance of KIT Mutations in AML With inv(16) and t(8;21). J Clin Oncol 2006; 24:3904-3911.

- 110 patients with de novo CBF AML, 61 with inv(16) and 49 with t(8;21).

- All received cytarabine with daunorubicin alone or with daunorubicin + etoposide +/- multidrug resistance modulator PSC-833. CR received postremission HIDAC x 4 cycles.

- KIT mutations subdivided into mutKIT8 and mutKIT17 based on exon affected.
Mutations in KIT were found in 18 (29.5%) of those with inv(16).

92% patients with inv(16) achieved complete remission. In total, 5 year CIR and OS rates were 36% and 62%.
Paschka et al. Adverse Prognostic Significance of KIT Mutations in AML With inv(16) and t(8;21). J Clin Oncol 24:3904-3911.

Figure 1: Cumulative incidence of relapse of patients with inv(16) according to mutational status of KIT. (A) Patients with wild-type KIT (wtKIT/29%) versus those with any type of KIT mutation (mutKIT/56%). (B) Patients with wtKIT versus those with a mutation in exon 17 (mutKIT17) and those with a sole mutation in exon 8 (mutKIT8).

Figure 2: Predicted OS of patients with inv(16) according to mutational status of KIT. The 2- and 5-year survival estimates for the wtKIT group are 81% and 74% versus 44% and 32% for the mutKIT group, respectively.
AK case

- Treatment-related AML with inv(16).
  - Further risk stratification: Positive for mutKIT17 (D816).

- She would be expected to have a similar likelihood of CR with inversion(16) TAML compared to inversion(16) de novo AML.
  - However, relapse rate would be expected to be greater given her age > 35.
  - Higher risk of relapse with positive mutKIT17.
AK case

- Patient received 7+3 with cytarabine 100 mg/m² and daunorubicin 60 mg/m².
- High likelihood of CR (>90%) with this regimen.

- D14 and D28 marrows were without evidence of residual leukemic cells.
Patient received 7+3 because she was ineligible for a clinical trial given her recent history of malignancy.

Why give a therapy such as G-CLAC if 7+3 has such a high CR rate?

In another, younger patient with inversion(16) who did not have KIT mutation checked, patient was entered into G-CLAC study. Is this ethical given the high CR rate?
Dr. Estey
Why Give GCLAC to INV(16)?

- Goal is to produce a long CR, not just CR
- Induction Rx affects CR duration
<table>
<thead>
<tr>
<th>Induction</th>
<th>In CR</th>
<th>Pts</th>
<th>4 Year RFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDAC</td>
<td>SDAC</td>
<td>78</td>
<td>23%</td>
</tr>
<tr>
<td>SDAC</td>
<td>HDAC</td>
<td>53</td>
<td>14%</td>
</tr>
<tr>
<td>HDAC</td>
<td>HDAC</td>
<td>34</td>
<td>34%</td>
</tr>
<tr>
<td>SDAC</td>
<td>SDAC</td>
<td>48</td>
<td>4%</td>
</tr>
<tr>
<td>SDAC</td>
<td>HDAC</td>
<td>42</td>
<td>17%</td>
</tr>
<tr>
<td>HDAC</td>
<td>HDAC</td>
<td>32</td>
<td>25%</td>
</tr>
</tbody>
</table>
## 3-Yr RFS By Induction & Post CR Rx

<table>
<thead>
<tr>
<th>Post CR</th>
<th>Intensive Induct</th>
<th>Standard Induct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo</td>
<td>0.36</td>
<td>0.30</td>
</tr>
<tr>
<td>Auto</td>
<td>0.58</td>
<td>0.40</td>
</tr>
<tr>
<td>Allo</td>
<td>0.77</td>
<td>0.49</td>
</tr>
</tbody>
</table>

CCG Blood 1996;87: 4979-89
Effect of MRD Prior to Ablative HCT (Walter et al. JCO in press)
Was ATRA- ATO Trial Ethical?

- If, after entry of each cohort of 6 pts >90% probability that rates of CR or PCR neg at 6 mos “too low”, STOP ACCRUAL
- Too low means < 80% CR rate and < 77% PCR negativity rate at 6 mos. (L-ATRA data)
- If true CR rate 60% trial stops after median 12 pts (if < 60% stops after fewer pts)
- 12 pts X 60% CR = 7 CR vs. 10 CR if historical CR rate; “potential cost of trial” = 3 pts