Therapy-Related AML

Lymphoma Tumor Board

July 7, 2017
ACUTE MYELOGENOUS LEUKEMIA

MALIGNANCY INVOLVING THE MYELOID LINE OF PRECURSOR CELLS

> 20% BLASTS IN BONE MARROW

BLAST!

AUER RODS

AUER RODS STINK!

TYPICALLY AFFECTS ADULTS GREATER THAN 65 YEARS OF AGE

LEUKOSTASIS, CNS SYMPTOMS, DISSEMINATED INTRAVASCULAR COAGULATION (DIC)

THE AMAZING LURE
# Therapy-related AML (T-AML)

## Table 1: 2008 WHO classification of acute myelogenous leukemia (AML)

### AML with recurrent genetic abnormalities

- AML with t(8;21)(q22;q22); RUNX1-RUNX1T1
- AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); CBFB-MYH11
- AML with t(15;17)(q22;q12); PML-RARA
- AML with t(9;11)(p22;q23); MLLT3-MLL
- AML with t(6;9)(p23;q34); DEK-NUP214
- AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); RPN1-EVI1
- AML (megakaryoblastic) with t(1;22)(p13;q13); RBM15-MKL1
- Provisional entity: AML with mutated NPM1
- Provisional entity: AML with mutated CEBPA

### Therapy-related myeloid neoplasms

### AML, not otherwise specified

- AML with minimal differentiation
- AML without maturation
- AML with maturation
- Acute myelomonocytic leukemia
- Acute monocytic/myeloid leukemia
- Acute erythroid leukemias
  - Pure erythroid leukemia
  - Erythroleukemia, erythroid/myeloid
- Acute megakaryoblastic leukemia
- Acute basophilic leukemia
- Acute panmyelosis with myelofibrosis

### Myeloid sarcoma

**WHO = World Health Organization**


Therapy-related AML (t-AML)

- Clinical syndrome that occurs after cytotoxic and/or radiation therapy
- ~10% of all AMLs arise after exposure to chemotherapy and/or radiation for a primary malignancy or autoimmune disease, and are called t-AML
- Considered to have inferior outcome compared with de novo AML
- Latency period between diagnosis of primary malignancy and t-AML can range from a few months to several years
  - Depends on the type of treatment that was received for the primary malignancy
- t-AML associated with abnormal cytogenetics more commonly than de novo AML
- 2 subtypes of t-AML are described, but are not subcategorized by WHO classification:
  - Most common subtype occurs after exposure to alkylating agents and/or radiation
    - Latency period of 5-10 years
    - Unbalanced cytogenetic abnormalities
    - Loss of all or some parts of chromosome 5 and or 7
  - Less common subtype occurs after treatment with agents targeting topoisomerase II
    - Latency period of 1-5 years
    - Balanced chromosomal rearrangements involving MLL, RUNX1, and PML-RARA
Reference Case: Therapy-related myeloid neoplasm (acute myeloid leukemia)

Authors: Elizabeth L. Courville, MD

Category: Myeloid Neoplasms and acute leukemia (WHO 2016) > Acute Myeloid Leukemia > Therapy-related myeloid neoplasms

Description:
67 year old female with a history of breast cancer diagnosed 2 years prior to this biopsy and treated with cytotoxic chemotherapy. Therapy related myeloid neoplasms include therapy-related acute myeloid leukemia (t-AML), myelodysplastic syndrome (t-MDS), and myelodysplastic/myeloproliferative neoplasms (t-MDS/MPN). These neoplasms occur as late complications of cytotoxic chemotherapy and/or radiation therapy administered for a prior neoplastic or non-neoplastic disorder. Cytogenetic analysis of the bone marrow specimen in this case was abnormal, showing a t(6;11)(q27;q23) by karyotype and a MLL gene rearrangement in 90.5% of cells examined by FISH. A balanced chromosomal translocation is seen in about 25% of cases of therapy-related myeloid neoplasm. Such cases are generally associated with a short latency period, most often present as overt AML without a preceding myelodysplastic phase, and are associated with prior topoisomerase II inhibitor therapy.
Therapy-related myeloid neoplasm (Acute myeloid leukemia)

Peripheral blood smear

The peripheral blood shows anemia, thrombocytopenia, and a leukocytosis with numerous circulating blasts.
Therapy-related myeloid neoplasm (Acute myeloid leukemia)

Aspirate smear and touch preparation

Blasts are increased on differential count of the aspirate smear (44%).
Therapy-related myeloid neoplasm (Acute myeloid leukemia)

Aspirate smear and touch preparation

Blasts are increased on differential count of the aspirate smear (44%).
Therapy-related myeloid neoplasm (Acute myeloid leukemia)

Trephine Core

The trephine core is hypercellular with frequent blasts. Scattered megakaryocytes are notable for widely separated nuclear lobes.
Risk factors for therapy-related AML/MDS

Variables confounding accurate diagnosis of therapy-related AML or MDS (red circle).

- Cancer therapy
- Prior cancer
- Other exposures
- Age
- Genetic predisposition
Risk factors for therapy-related AML/MDS

Lifestyle:
- Smoking
- Alcohol
- Diet
- Hair dye

Environment/Occupation:
- Air pollution
- Magnetic fields
- Ionizing radiation
- Chemicals
- Benzene
- Virus

Primary Cancer

Treatment:
- Alkykating agents
- Topoisomerase II inhibitors
- Radiation therapy

Host factors:
- Genetic diseases (Down S., Bloom S., etc.)
- Enzymatic polymorphisms
- DNA repair polymorphisms
- Other

Primary Cancer and t-AML/MDS

t-AML attributable to cytotoxic drugs falls into two general classes


<table>
<thead>
<tr>
<th>Class</th>
<th>GST</th>
<th>CYP</th>
<th>DNA repair</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating agents</td>
<td>GSTT1 GSTM1 GSTP1</td>
<td>CYP2B6 CYP2C19 CYP3A4</td>
<td>MGMT BER (RAD51 XRCC3)</td>
</tr>
<tr>
<td>Mechlorethamine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Melphalan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Busulphan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BCNU, CCNU</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topoisomerase I inhibitors</td>
<td>Topotecan</td>
<td>CYP3A</td>
<td>NHEJ</td>
</tr>
<tr>
<td></td>
<td>Irinotecan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topoisomerase II inhibitors</td>
<td>Mitoxantrone</td>
<td>(GSTP1)</td>
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</tr>
<tr>
<td></td>
<td>Daunorubicin</td>
<td></td>
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<tr>
<td></td>
<td>Doxorubicin</td>
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<td></td>
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<tr>
<td></td>
<td>Etoposide</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Teniposide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ionizing radiation</td>
<td></td>
<td>(RAD51 XRCC3)</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Anti-cancer agents and detoxification/DNA repair.
Risk factors for t-AML/MDS after Rx for Hodgkin lymphoma

Table 2.

Risk of MDS/AML in patients receiving chemo/radiotherapy for Hodgkin’s lymphoma, according to treatment.

<table>
<thead>
<tr>
<th>References</th>
<th>No. of pts</th>
<th>Therapy</th>
<th>Cases of t-MDS/AML</th>
<th>Cumulative Risk (%)</th>
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</thead>
<tbody>
<tr>
<td>Brusamolino et al,36</td>
<td>348</td>
<td>RT</td>
<td>2</td>
<td>0.3</td>
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<tr>
<td>Josting et al,37</td>
<td>677</td>
<td></td>
<td></td>
<td>0.6</td>
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<tr>
<td>Brusamolino et al,36</td>
<td>124</td>
<td>MOPP</td>
<td>3</td>
<td>2.2</td>
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<tr>
<td>Josting et al,37</td>
<td>1775</td>
<td>COPP*ABVD</td>
<td>15</td>
<td>0.8</td>
</tr>
<tr>
<td>Brusamolino et al,36</td>
<td>277</td>
<td>MOPP+RT (involved field)</td>
<td>18</td>
<td>10.2 (15 yrs)</td>
</tr>
<tr>
<td>Delwall et al,36</td>
<td>374</td>
<td>MOPP+RT (extended field)</td>
<td>5</td>
<td>2.4 (15 yrs)</td>
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<tr>
<td>Delwall et al,36</td>
<td>36</td>
<td></td>
<td>4</td>
<td>13.9 (15 yrs)</td>
</tr>
<tr>
<td>Brusamolino et al,36</td>
<td>24</td>
<td>ABVD</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Josting et al,37</td>
<td>304</td>
<td></td>
<td>1</td>
<td>0.3</td>
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<tr>
<td>Brusamolino et al,36</td>
<td>129</td>
<td>ABVD*RT (involved field)</td>
<td>1</td>
<td>0.8</td>
</tr>
<tr>
<td>Delwall et al,36</td>
<td>279</td>
<td>ABVD*RT (extended field)</td>
<td>2+1 (ALL)</td>
<td>1.2</td>
</tr>
<tr>
<td>Delwall et al,36</td>
<td>36</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Josting et al,37</td>
<td>500</td>
<td>BEACOPP baseline</td>
<td>2</td>
<td>0.4</td>
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<tr>
<td></td>
<td>460</td>
<td>BEACOPP escalated</td>
<td>8</td>
<td>1.7</td>
</tr>
</tbody>
</table>

RT: radiotherapy; MOPP: mechlorethamine, vincristine, procarbazine, prednisone; ABVD: Adriamycin, bleomycin, vinblastine, dacarbazine; COPP: cyclophosphamide, vincristine, procarbazine, prednisone; BEACOPP: bleomycin, etoposide, cyclophosphamide, vincristine, procarbazine, prednisone.

Risk factors for t-AML/MDS after Rx for breast cancer

Distribution of cytogenetic abnormalities in t-AML

A

- Normal karyotype: 25%
- inv(3) or t(3:3): 1%
- t(v;11)(v;q23): 4%
- t(9;11): 11%
- inv(16) or t(16;16): 8%
- t(8;21): 5%
- t(15;17): 2%
- Other abnormalities: 9%
- MDS-related cytogenetic abnormalities: 35%

B

- Normal karyotype: 49%
- inv(3) or t(3:3): 2%
- t(6;9): 1%
- t(v;11)(v;q23): 2%
- t(9;11): 1%
- inv(16) or t(16;16): 6%
- t(8;21): 5%
- t(15;17): 4%
- Other abnormalities: 14%
- MDS-related cytogenetic abnormalities: 16%


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Frequency and distribution of cytogenetic abnormalities in AML patients exhibiting at least one abnormality

A
- complex: 58%
- monosomaly: 51%
- -5 or 5q-: 33%
- -7 or 7q-: 42%
- +8: 15%
- abnl(12p): 18%
- abnl(17p): 32%
- abnl(20q): 13%

B
- complex: 36%
- monosomaly: 30%
- -5 or 5q-: 25%
- -7 or 7q-: 26%
- +8: 25%
- abnl(12p): 13%
- abnl(17p): 11%
- abnl(20q): 9%

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Different genetic pathways in t-MDS and t-AML

Primary Aberrations

-7, 7q -

-5

5q -

-7, 7q -

-3p -

3p -

3p -

3q - 12p -

Rearranged MLL

t(11q23)

Rearranged AML1 and CBFB

t(8;21) and inv(16)

Rearranged RARA

t(15;17)

Rearranged NUP98

t(11p15)

Additional Aberrations

Normal Karyotype

Internal Dupl. FLT3 and MLL

Secondary Aberrations

RAS Mutations

Methylated p15 Promotor

+8

-18


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Treatment of t-AML

• Limited data are available – optimal treatment of t-AML is uncertain
• Supportive care is favored along with clinical trials
• In select cases, aggressive therapy such as allogenic hematopoietic cell transplantation (HCT) may be an option and can be curative
• Important considerations:
  • Patient age
  • Co-morbidities
  • Performance status
  • Persistence of primary malignant disease
  • Tumor karyotype
  • If patient is a candidate for induction chemotherapy, tumor cytogenetics can help determine the prognosis and chances of completing induction therapy.

One commonly used system for estimating prognosis based on karyotype is:

• Favorable – t(8;21), inv(16), t(15;17)
• Intermediate – Normal, t(9;11), other abnormalities not described as favorable or unfavorable
• Unfavorable – 3q21q26 abnormalities, del 5q, del 7q, t(6;9), other 11q23 abnormalities, 12p abnormalities, 17p abnormalities, monosomies 5 or 7, trisomies 8 or 13, or complex aberrant karyotypes described as at least three unrelated abnormalities excluding cases with t(8;21), inv(16), and t(15;17)
Decision tree for the management of therapy-related myeloid neoplasms

Clinical and morphological diagnosis of t-MDS/t-AMLπ

- Good performance status
  - t-APL
    - ATRA + chemotherapy (+ As2O3)
  - Inv(16) or t(8;21)
    - Treat as per de novo AML
      - Standard induction + high-dose cytarabine consolidation
  - Normal karyotype
    - Treat as per de novo AML
      - Standard induction
    - Standard induction
  - Unfavorable cytogenetics
    - Investigational therapy or allogeneic HCT
  - Supportive care

- Poor performance status
  - Standard induction
  - Allogeneic HCT or consolidation chemotherapy
Kaplan-Meier survival analysis of overall and relapse-free survival in 2853 patients with de novo AML or t-AML.
Kaplan-Meier survival analysis of 65 consecutive patients with t-AML after allogeneic transplantation

Figure 1. OS of all patients with t-AML/MDS.

Relapse and death in CR in t-AML and de novo AML


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Influence of AML type and postremission Rx on CID and CIR

Auer Rods

References


• Robert Peter Gale M, PhD, FACP, F. Owen Hoffman, PhD, John M. Bennett, MD Therapy-Related AML and MDS: Who Really Has It? The Hematologist. 2015;12(4).

• http://imaging.ubmmedica.com/all/editorial/cancernetwork/cmhb/29_Table1_large.png
• https://en.wikipedia.org/wiki/Acute_myeloid_leukemia
• https://imagebank.hematology.org/
• www.medcomic.com