Therapy-Related Myeloid Neoplasms (t-MN)

5/17/2011
Outlines

• Present a clinical case as an example of therapy-related myeloid neoplasm

• Discuss therapy-related myeloid neoplasm

Cervical node biopsy
Dx: Nodular lymphocyte predominant Hodgkin lymphoma

Staging bone marrow aspirate and biopsy at that time was negative

R-CHOP completed in November 2007

June 2008, the Hodgkin lymphoma recurred in mesenteric lymph node

He received 6 cycles of ABVD and MOPP chemotherapy

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In October 2010, follow-up CBC: WBC 0.7 k/uL (ANC 0.2), HGB 9.9 g/dL, PLT 115 k/uL
Peripheral blood

WBC 0.7 k/uL
HGB 9.9 g/dL
PLT 115 k/uL
24.6% Blasts
0.4% Promyelocytes
7.2% Granulocytic precursors
46% Erythroid precursors
19% Lymphocytes
1% Eosinophils
0% Basophils
0.8% Monocytes
1% Plasma cells
46,XY,+1,r(1)(p36q44)x2, -10,t(11;19)(q23;p13.3)[19/20]
Molecular Studies

- Negative for CEBPA mutation
- Negative for NPM1 mutation
- Negative for a FLT3 Gene Mutation (ITD, D835)
- Negative for KIT D816V mutation

Diagnosis

Therapy-related acute myeloid leukemia, associated with cytogenetic translocation t(11;19)(q23;p13.3)
Therapy-Related Myeloid Neoplasms (t-MN)

• A late complications of cytotoxic chemotherapy and/or radiation therapy administered for a prior neoplastic or non-neoplastic disorders

World Health Organization (WHO) ‘Classification of Tumours of Haematopoietic and Lymphoid Tissues’ 2008

• The term t-MN includes t-AML, t-MDS, and t-MDS/MPN
• t-MN account for 10 to 20% of all cases of AML, MDS, and MDS/MPN
t-MN Epidemiology

- Therapy-related MNs account for 10-20% of all cases of AML, MDS and MDS/MPN

- The incidence varies according to the underlying disease and the treatment strategy

- All age groups are affected

- The risk for those treated with:
  - Alkylating agents or radiation therapy generally increases with age
  - Topoisomerase II inhibitors is similar across all ages
t-MN Epidemiology

- The majority of patients (70%) with t-MNs present with MDS or AML transformed from MDS

- Median latency period of 5–10 years following:
  - Alkylating agents
  - Immunosuppressive drugs
  - Radiotherapy

- Patients frequently exhibit marked peripheral blood cytopenias and dysplastic features

- Structural aberrations involving chromosomes 5 and 7 or a complex karyotype are common
20 to 30% of patients with t-MNs present with overt AML

Leukemic cells predominantly exhibit a monocytic or myelomonocytic phenotype

Median latency period of 1-5 years following:
- Topoisomerase-II-inhibitors

Balanced chromosomal translocations including 11q23 and 21q22 rearrangements or abnormalities such as t(15;17)(q22;q12) and inv(16)(p13q22) are common
What class of chemotherapy did our patient receive?

CHOP, ABVD, MOPP

- Cyclophosphamide
- Dacarbazin
- Mechloretamine
- Procarbazine
- Alkylating agents
- Doxorubicin
- Topoisomerase II inhibitor
- Vincristine
- Vinblastine
- Anti-microtubule agent
- Bleomycin
- Glycopeptide antibiotic
Because many patients will be receiving multiple lines of treatment including several classes of chemotherapy compounds, the WHO has therefore abandoned its former classification into alkylating agent or topoisomerase-II-inhibitor associated therapy-related disease.
What are the risks for t-MN?

• Prior therapeutic exposure
• Genetic susceptibility

WHO, Classification of Tumours of Haematopoietic and Lymphoid Tissues 2008
Agents Implicated in the Development of t-MN

- **Alkylating agents**
  - Busulfan, Carboplatin, Carmustine, Chlorambucil, Cisplatin, Cyclophosphamide, Dacarbazine, Dihydroxybusulfan, Lomustine, Mechlorethamine, Melphalan, Mitomycin C, Procarbazine, Semustine, Thiotepa

- **Topoisomerase II inhibitors**
  - Bimolane, Dactinomycin, Daunorubicin, Doxorubicin, 4-Epi-doxorubicin, Etoposide, Mitoxantrone, Razoxane, Teniposide

- **Antimetabolites**
  - Fludarabine, 6-Mercaptopurine, Methotrexate

- **Antimicrotubule agents**
  - Docetaxel, Paclitaxel, Vinblastine, Vincristine

- **Radiotherapy**

- **Growth factors**
  - Granulocyte CSF and granulocyte-macrophage CSF in context of radiochemotherapy

- **Immunomodulator**
  - Azathioprine

H Sill et al. 2011
AA transfer methyl groups (CH3 or -CH2-CH3) to oxygen or nitrogen atoms of DNA bases resulting in highly mutagenic DNA base lesions (O^6-methylguanine and N^3-methylcytosine)
O⁶-methylguanine-DNA methyltransferase (MGMT) is an enzyme that perform damage reversal in a one step reaction
Alkylating Agents

O\textsuperscript{6}-methylguanine

DNA replication → Base Mis-pairing → DNA double strand breaks (DSBs) → Cytotoxicity and mutagenicity (translocations, inversions, insertions and loss of heterozygosity)

AA can also form interstrand crosslinks causing stalling of the replication forks

H Sill et al. 2011
• DNA topoisomerases are critical enzymes responsible for relaxing supercoiled DNA, thus allowing DNA replication to occur.

Topoisomerases bind covalently to the DNA strand and create transient single (type I topo) and DSBs (type II topo).

H Sill et al. 2011
Topoisomerase Inhibitors

- Topoisomerase inhibitors block the release of topoisomerases from cleaved DNA, preventing re-ligation of the DNA strands and generating permanent DNA DSBs that trigger apoptosis.

- DNA DSBs are also highly mutagenic and can result in chromosomal deletions, insertions, inversions and translocations.
Anti-metabolites

- Antimetabolites are incorporated into DNA, thereby interfering with replication and leading to cell cycle arrest and apoptosis.

- Azathioprine, a widely used immunosuppressant, is metabolized to 6-thioguanine. Once placed in the newly synthesized DNA strand, 6-thioguanine is prone to methylation and formation of the highly mutagenic base lesion 6-thio-methylguanine that closely resembles the O\(^6\)methylguanine lesion induced by alkylating agents.

- Azathioprine treatment frequently harbor partial or complete loss of chromosomes 5 and 7.
Ionizing Radiation

• The high incidence of myeloid leukemias in Nagasaki and Hiroshima atomic bomb survivors firmly established the causal relation between ionizing radiation and hematological malignancies

• Exposure of cells to ionizing radiation results in the formation of reactive oxygen species (ROS) through radiolysis of water molecules. ROS (hydroxyl radicals, superoxide radicals and hydrogen peroxide) are highly reactive molecules that can oxidize or deaminate DNA bases and increase the frequency of DNA double strand breaks (DSBs)
Recent reports have expressed concerns about an increased risk of developing t-MNs in patients receiving G-CSF during chemotherapy.

Two mechanisms have been implicated in the G-CSF-mediated promotion of t-MNs:

- First, G-CSF-induced production and release of ROS by bone marrow neutrophils may result in increased DNA damage and mutation rates in HSPC (Touw and Bontenbal, 2007).

- Second, repeated application of G-CSF results in a continuous displacement of these cells from their protective bone marrow environment, which may render them more susceptible to genotoxic stress (Trumpp et al., 2010).
Granulocyte-Colony Stimulating Factor

• A recent meta-analysis, evaluated the risk of t-MNs in patients undergoing chemotherapy randomly assigned to receive G-CSF, the risk increase for developing t-MN was about 0.43% (Lyman et al., 2010)

• However, this meta-analysis indicated that the administration of G-CSF for the treatment of chemotherapy-related neutropenia and its complications benefits a substantial proportion of patients and outweighs the increased t-MN risk
Genetic Susceptibility

• Only a small fraction of patients exposed to cytotoxic therapy develop t-MNs

• Animal models: treating different inbred mouse strains with the alkylating agent ENU showed: a high interstrain variability of therapy-induced hematologic malignancies

• Heritable predisposition, due to enzymatic polymorphisms of DNA repair or drug metabolism have been hypothesized

Lyman et al., 2010
Genetic Susceptibility

- DNA damage, due to normal metabolic processes inside the cell, occurs at a rate of 1,000 to 1,000,000 molecular lesions per cell per day (constitutes only 0.000165% of the human genome)  

- Rate of DNA damage = Rate of repair

- A high number of double-strand DNA (DSBs) breaks arises following chemotherapy or exposure to radiation
RAD51 and XRCC3 are the central genes involved in the repair of DSBs.

Polymorphisms in these genes have been linked to an increased risk of developing t-MDS/AML and with abnormalities of chromosomes 5 and/or 7.
Phase I drug-detoxifying enzymes: The cytochrome P450 (CYPs) family is accounting for about 75% of the total number of different metabolic reactions

- CYP3A4-V (CYP3A4) and CYP1A1*2A (CYP1A2)
- Associated with an increased risk of t-MDS/AML
Genetic Susceptibility

- Phase II drug-detoxifying enzymes: The metabolizing-conjugating enzymes
  - NQO1*2 (NAD(P)H:quinone oxidoreductase, NQO1) and GSTM1, GSTT1, and GSTP1 variants of (Glutathione S-transferase, GST)
  - Associated with abnormalities of chromosomes 5 and/or 7 and an increased risk of developing t-MDS/AML
t-MN Morphology

- The majority of patients present with t-AML/t-MDS associated with multilineage dysplasia (alkylating agents and/or radiotherapy)

The PB
- one or more cytopenias
- Anemia is almost always present
- RBC (macrocytosis and poikilocytosis)
- Dysgranulopoiesis
- Basophilia is frequently present

The BM
- May be hypercellular, normocellular or hypocellular,
- Slight to marked BM fibrosis occurs in approximately 15% of cases
- Dysgranulopoiesis and dyserythropoiesis and dysmegakaryopoiesis are present in most patients
- Ring sideroblasts are reported in up to 60% of cases

WHO, Classification of Tumours of Haematopoietic and Lymphoid Tissues 2008
50% of patients presenting with a myelodysplastic phase will have <5% BM blasts

About 5% of patients have features of MDS/MPN, such as CMML

In 20-30% of cases (Topo II inh), the first manifestation of therapy-related myeloid neoplasm is overt acute leukemia (Blasts ≥ 20%) without a preceding MDS

Cases of lymphoblastic leukemia (ALL) also occur (5%), usually associated with a t(4;11)(q21;q23)

Recent WHO classification does not distinguish the different forms of t-MN
Subclassification of MDS or separating t-MDS from t-AML according to the number of blasts present in the bone marrow may not be relevant clinically.

Genetics of t-MN

- Over 90% of patients with t-MN will have an abnormal karyotype.

- Patients treated by alkylating agents and/or radiotherapy (70%) show structural abnormalities (-5, -7, 5q-, 7q-) and complex karyotype [e.g. del(13q), del(20q), del(11q), del(3p), -17, -18, -21, +8].

- Patients treated by topoisomerase II inhibitors (30%) show balanced chromosomal translocations that involve rearrangements of 11q23 [including t(9; 11)(p22;q23) and t(11;19)(q23;p13)], 21q22 [including t(8;21)(q22;q22) and t(3;21)(q26.2;q22.1)] and other abnormalities such as t(15;17)(q22;q12) and inv(16)(p13.1q22).
Therapy-Related Versus De Novo Myeloid Neoplasms

• According to the WHO classification, the distinction of t-MNs from de novo myeloid malignancies is solely based on a patient’s history but not on specific molecular, cytogenetic or cellular markers

• Myeloid neoplasms associated with occupational or environmental exposure to leukemogenic agents show similarities to t-MNs
  – MDS and AML following occupational benzene exposure show a tendency to develop chromosome 5 and 7 abnormalities
Interestingly, high-risk de novo MDS/AML cases also share biological and clinical features with t-MNs including:

– Chromosomal 5 and/or 7 abnormalities
– Low response rates to:
  • intensive chemotherapies
  • Hematopoietic stem cell transplantation
Therapy-Related Versus De Novo Myeloid Neoplasms

- Acute toxicity (chemo-/radiotherapy)
- DNA damage
- Cancer predisposing genetic variants
- therapy-related myeloid neoplasms

- Chronic toxicity (environmental/occupational?)
- MDS/AML predisposing genetic variants
- high-risk \textit{de novo} MDS/AML
Therapy-related versus de novo myeloid neoplasms

**t-related**
- 11q23: 3%
- inv(16): 2%
- t(8;21): 3%
- 5+7: 22%
- others: 32%

**De novo**
- NL: 8%
- Ch. 5: 21%
- NL: 20%
- Ch. 7: 5%
- Ch. 5: 5%
- t(15;17): 9%
- inv(16): 5%
- t(8;21): 10%
- 11q23: 5%
- others: 32%

**References**
- Smith SM, et al. 2003
- WHO CTHLT, 2008
t-Related Acute Promyelocytic Leukemia (t-APL)

- The t-APL represents approximately 20% of all cases of APL

- It most commonly follows treatment of breast carcinoma, presumably owing to a higher number of patients receiving anthracycline-based therapies

- The majority of cases develop fewer than 3 years after the primary therapy

- There is no preleukemic phase

- The presentation and outcome are generally similar to cases of de novo APL
Prognosis of t-MN

• Generally poor

• Strongly influenced by:
  – the associated karyotypic abnormality
  – the comorbidity of the underlying malignancy or disease for which cytotoxic therapy was initially required

• Overall, 5-year survival of less than 10% is commonly reported
Prognosis of t-MN

- Cases associated with abnormalities of Ch. 5 and/or 7 and a complex karyotype have a particularly poor outcome with a median survival time of less than one year regardless of whether they present as overt acute leukemia or as t-MDS.
## Take Home Message

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Thank you
Animal models: treating different inbred mouse strains with the alkylating agent ENU showed:

- a high interstrain variability of therapy-induced solid and hematologic malignancies
- A set of loci and candidate genes were implicated
- The transcription factor Early Growth Receptor 1 (EGR1) has been identified as a candidate tumor suppressor gene located in the commonly deleted region of chromosome 5
- Egr1 knockout mice display only minor hematopoietic abnormalities
- However, following treatment with the alkylating agent ENU, 40% of Egr1-/- and 33% of Egr1+/- mice develop a myeloproliferative disorder, as compared with only 13% of wild-type mice (Lai et al., 2001).