Therapy-Related AML/MDS With A Philadelphia Chromosome

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2 November 2007

CASE ID# 176
Initial Presentation

HPI:
• 43 year old male presented in December 2002 with fatigue and 20 lb weight loss since July 2002.

PAST MEDICAL HISTORY:
• Mild psoriasis.

MEDICATIONS: None.

FAMILY HISTORY:
• Father died of lung cancer.
• Mother has history of diabetes mellitus type II.
• Brother has history of TTP.

PHYSICAL EXAM: Unremarkable
Initial Presentation

ADMISSION LABORATORY FINDINGS:

- WBC $19.1 \times 10^9$/L
  - 54% neutrophils, 4% myelocytes, 1% metamyelocytes, 19% lymphocytes, 2% monocytes, 2% eosinophils, 17% blasts, and 1% promonocytes
- Hgb 9.4 g/dL
- Platelets $341 \times 10^9$/L

Pathology:
Bone Marrow Biopsy Performed
Diagnostic Marrow Findings

- **Aspirate differential**
  - 56% myeloid precursors
  - 2% erythroid precursors
  - 7% lymphocytes
  - 2% monocytes
  - 1% eosinophils
  - 0% basophils
  - 1% plasma cells
  - 4% promyelocytes
  - **27% blasts**

  ~20% of all cells are positive for nonspecific esterase.

  ~ 25% of blast cells are positive for myeloperoxidase.

December 2002 (400x)
Flow Cytometry

- CD33+, CD13+, HLA-DR+, CD117+/-, TdT+/-, CD34-, MPO-, CD4dim+, CD7dim+ myeloblasts (23% of total events).
47,XY,+21[5]/46,XY[14]
Diagnosis: WHO Classification

ACUTE MYELOID LEUKEMIA
NOT OTHERWISE CATEGORIZED:
ACUTE MYELOMONOCYTIC LEUKEMIA (FAB M4)
**Treatment and Response**

**Induction:**
Study protocol CALGB 19808.

**Consolidation:** 1 cycle high dose of etoposide & high dose cytarabine

**Laboratory (July to Dec 2003):**
- WBC: 1.5-5.5 x 10⁹/L
- Hgb: 8.8-13.1 g/dL
- Platelets: 39-89 x 10⁹/L

**Complete remission**

**Bone marrow harvest**

**Day 100 s/p transplant**
Trilineage hematopoiesis.
No evidence of acute leukemia

**Cytogenetics:** XY[20]
January 2004

HPI:

• Patient reported increased fatigue and leg weakness.

LABORATORY FINDINGS:

• WBC 10.0 x 10^9/L
  • 66% neutrophils, 8% myelocytes, 1% metamyelocytes, 2% promyelocytes, 10% lymphocytes, 3% monocytes, 0% basophils, and 10% blasts.
  • 12 nRBCs/100 WBC
• Hgb 7.9 g/dL
• Platelets 106 x 10^9/L
January 2004 Pathology

- Bone Marrow Biopsy:
  - Limited sample
  - Multilineage dysplasia noted with 12% blasts.
  - Flow cytometry showed 4% myeloblasts
  - Cytogenetics attempted but no metaphases for analysis.

- Clinically followed over next few months.
  - Peripheral blood counts remained low, but stable.
- Repeat biopsy in April 2004
April 2004 Pathology

WBC: 7.6 x 10⁹/L

- 88% neutrophils, 3% myelocytes, 3% metamyelocytes, 4% lymphocytes, 0% basophils, **2% Blasts**
- 4 nucleated RBC/100 WBC.

Hgb: 8.8 g/dL
Platelets: 58 x 10⁹/L
Diagnostic Marrow Findings

- Aspirate differential
  - 73% myeloid precursors
  - 16% erythroid precursors
  - 1% lymphocytes
  - 0% basophils
  - 1% promyelocytes
  - 9% blasts

The blast count vary in areas ranging from 5 to 15%.
Flow Cytometry

- CD33+, CD13+, HLA-DR+, CD117+, TdT-, CD34-, MPO+/-, CD4-, CD7- myeloblasts (6% of total events).
46, XY, der(1)inv(1)(p13q42)del(1)(q43), t(9;22)(q34;q11.2)[15]/46, XY[5]
Metaphase FISH

BCR/ABL t(9;22)

BCR 22q11.2

ABL 9q34

ish der(9)(ABL+,BCR+),der(22)(BCR+,ABL+)
Clinical Course

Two weeks after bone marrow biopsy presented with worsening fatigue.

LABORATORY FINDINGS:

• WBC 86.3 x 10^9/L
  • 48% blasts
• Hgb 7.0 g/dL
• Platelets 66 x 10^9/L
Diagnosis: WHO Classification

Therapy-related AML / MDS with Philadelphia chromosome.
Treatment

• Admitted for re-induction with intrathecal methotrexate, steroids, idarubicin and cytarabine.

• Gleevec started two weeks after re-induction.

• Died at day 39.
Philadelphia Chromosome in Therapy-related AML/MDS

• Late-occurring Philadelphia chromosome is rare in MDS and AML
  – Cytogenetic progression of an existing myeloid neoplasm
  – Therapy-related AML/MDS
Philadelphia Chromosome in Therapy-related AML/MDS

• Pedersen-Bjergaard et al. (1997) literature review:
  • Identified 8 cases of AML with Philadelphia chromosome following DNA topoisomerase II inhibitors
    • 2 following treatment for Hodgkin lymphoma
    • 6 following treatment for myeloid neoplasms
    • Some of these appear to represent relapsed AML with t(9;22) acquisition

• 4 of 20 Ph+AML patients in a multi-institutional series presented as secondary leukemia (Soupir et al. 2007)
  • 2/4 were karyotypically distinct from original leukemia, consistent with t-AML/MDS
  • In 1 case, the t(9;22) represented a secondary change in relapsed disease
  • In 1 case the relationship of the secondary leukemia to the original leukemia was indeterminate
Philadelphia Chromosome in Therapy-related AML/MDS

- Univariate and multivariate analysis of published cases of t-AML/MDS with balanced chromosome aberrations (Andersen et al. 1998)
  - 8.5% patients (N=328) with t-MDS/AML with balanced translocations following treatment with DNA topoisomerase II inhibitors had a t(9:22)
  - However, only 0.12% of all leukemias exhibiting t(9;22) are secondary Ph+ AML (Soupir et al. 2007).
Conclusion

• The difference in karyotype and morphology between the original AML and secondary AML in this case favor t-AML/MDS rather than acquisition of t(9;22) in relapsed AML.
  – BCR-ABL FISH attempted on original AML (biopsy block and aspirate smear) was unsuccessful.
  – Thus, a pre-existing Ph+ clone in the patient’s original leukemia cannot be entirely excluded.

2. Han, Jin-Yeong and Karl S. Theil. The Philadelphia chromosome as a secondary abnormality in inv(3)(q21q26) acute myeloid leukemia at diagnosis: confirmation of p190 BCR-ABL mRNA by real-time quantitative polymerase chain reaction. Cancer Genetics and Cytogenetics 2006; 165; 70-74


