Therapy-Related APL

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Patient History

- 63 y/o WM with resection of BFH in 1975
- March 2002
  - Bilateral pulmonary nodules
  - Right gluteal mass
- Biopsies showed MFH, myxoid type
- April through July 2002
  - Surgical resections and radiation therapy
Patient History
Gluteal Mass and Metastasis
Patient History

May 2005 - CT scan
- Soft tissue masses
  - Between esophagus and base of heart
  - Below left hemidiaphragm

June 2005 - received chemotherapy
- Ifosfamide (alkylating agent)
- Doxorubicin (topoisomerase II inhibitor)
- ET743 (topoisomerase I inhibitor)
  - Received 6 cycles
  - Completed in January 2006
Patient History

F/u visit in October 2006
- C/o easy bruisability and fatigue for 6 weeks
- CBC
  - WBC = 1.26K/mm$^3$
  - H/H = 10.7g/dL and 30.6%
  - Plt = 19K/mm$^3$
- Peripheral blood
  - Mild anisocytosis and poikilocytosis with scattered spherocytes
  - Scarcity of leukocytes
  - Markedly decreased platelets
  - 9% polys, 2%monos, 89%lymphs, 1% eos
Bone Marrow Aspirate

- Left-shifted myeloid series with predominance of promyelocytes and occasional blasts
- No Auer rods
- 3% polys, 3% bands, 14% lymphs, 17% erythroid, 8% myelocytes, 46% promyelocytes, 6% blasts, 3% plasma cells
Bone Marrow Aspirate
Bone Marrow Biopsy

- Markedly left-shifted myeloid series
- Prominent granularity in majority of cells
- Scattered erythrocyte precursors
- Rare megakaryocytes
Flow Cytometry

- Promyelocytes identified by CD45 vs SS
  - 57% of non-erythroid marrow elements
  - Positive for CD13, CD33, CD117, and CD38
  - Negative for HLA-DR, CD34, and CD15
Cytogenetics

- 46,XY,t(15;17)(q22;q21)[8]/46,XY[12]
- No del 5 or del 7
Molecular

- **FISH**
  - Fusion of PML/RARA signals in 113/252 (45%) of nuclei examined
Diagnosis

- Therapy-related acute promyelocytic leukemia (t-APL)
t-MDS and t-AML

- 10-30% of new cases of MDS and AML
- Same chromosomal abnormalities as de novo disease
- Two groups of t-AML
  - Progression from t-MDS
  - Overt t-AML
t-APL

- Rare complication of chemotherapy or radiotherapy
  - 200 cases reported in literature
  - 1\textsuperscript{st} seen in Chinese patients treated with bimolane for psoriasis

- Associated with topoiso merase II inhibitors
  - Anthracyclines
    - Daunorubicin, doxorubicin, and epirubicin
  - Anthracenedione
    - Mitoxantrone
  - Epipodophyllotoxins
    - Etoposide
t-APL

- Breakpoints previously described in t(15;17)
  - PML
    - Intron 3 (bcr3)
    - Exon 6 (bcr2)
    - Intron 6 (bcr1)
  - RARA
    - Intron 2

- European APL group
  - t-APL accounted for 22% of all APL
  - Attributed to increased use of mitoxantrone
    - Breast cancer (therapy in ~ 50% of cases)
DNA Breakpoints with Topoisomerase II Inhibitors

Study in 2005

- Compared breakpoints of t-APL patients and in vitro cleavage assays
- Found hot spot in 4 of 5 patients following mitoxantrone therapy
  - PML intron 6, positions 1482-1489
- Hot spot correlated with in vitro studies
  - Translocation hot spot was 9 times more likely to be used as compared to absence of drug

DNA Breakpoints with Topoisomerase II Inhibitors

- Breakpoints in RARA also identified
  - No two patients with same breakpoint
  - All breakpoints correlated with those produced with in vitro assays

- Other topoisomerase II inhibitors may result in hot spots in other genomic regions

t-APL

Study in 2007
- 69 patients with t-AML
- Better survival in t-AML associated with balanced translocations
- Still showed <50% survival at 12 months

Patient Follow-Up

- Treated with ATRA and idarubicin
- October 2007
  - CT of chest, abdomen, and pelvis
    - No evidence of metastatic disease
- CBC
  - WBC = 9.5K/mm$^3$ with normal differential
  - H/H = 14.1g/dL and 40.9%
  - Plt = 152K/mm$^3$
Summary

- Patient with MFH
- Treated with:
  - Doxorubicin (topoisomerase II inhibitor)
  - Ifosfamide (alkylating agent)
- Developed t-APL with t(15;17)
  - 16 months after onset of chemotherapy
- Now in remission for 12 months
References

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