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Is APL occurring as a therapy-related malignancy different from *de novo* APL?

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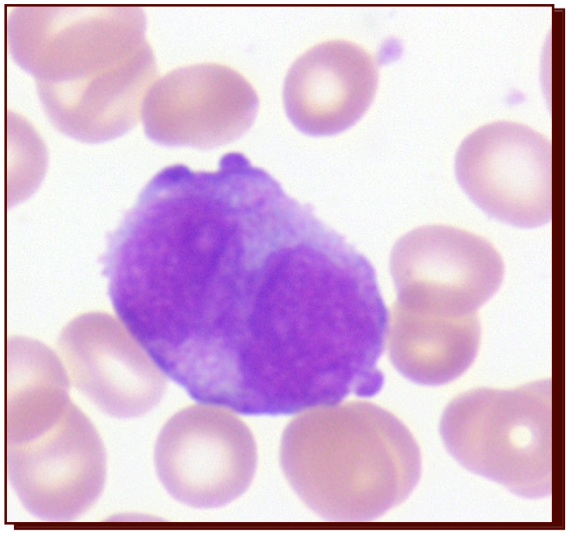
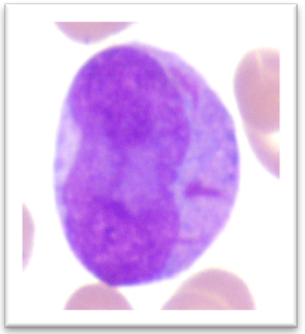
Case Presentation (1)

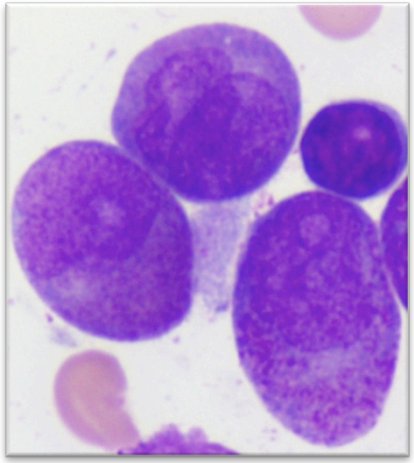
- 34 year old woman with localized breast cancer
- Lumpectomy, chest wall RT; Adriamycin + cyclophosphamide; Paclitaxel + G-CSF
- 3 years later – pancytopenia
- Bone marrow exam – APL
- 46XX,t(15;17),del(7q) in 11/20 cells
- *FLT3*-ITD+; *NPM1* negative
- Induction with ATRA + ATO → CR
- Hematologic & molecular remission



Case Presentation (2)



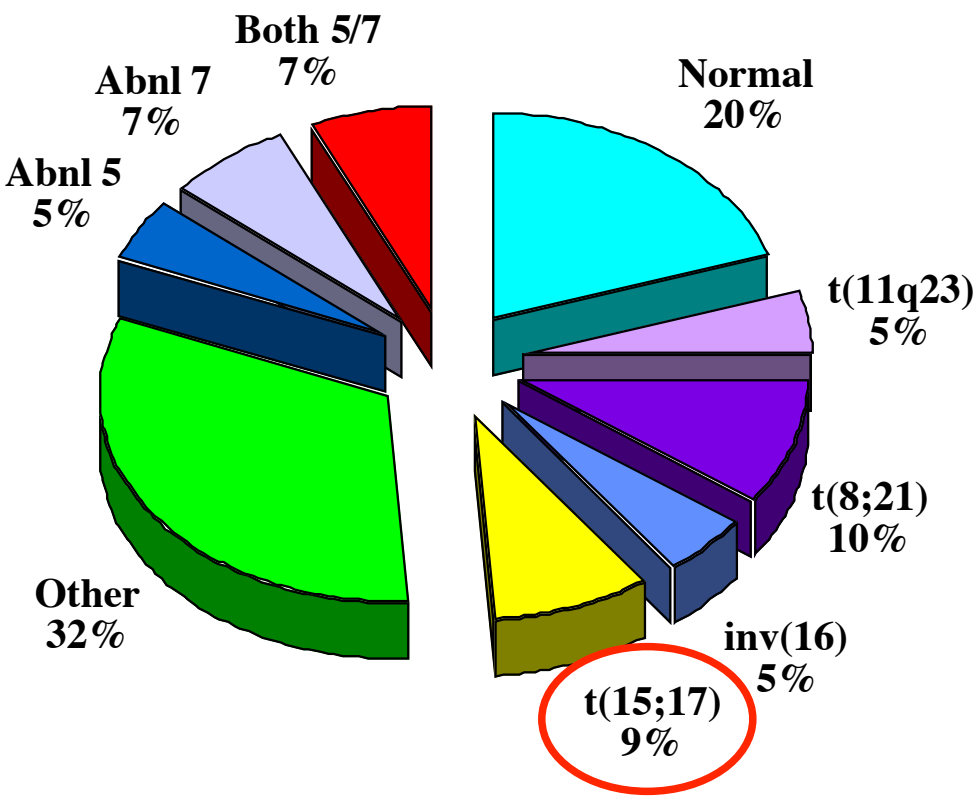
- 57 year old man with localized prostate cancer
- External beam radiation therapy (7000 cGy)
- 2.5 years later – pancytopenia
- Bone marrow exam – 40% cellular with 28% promyelocytes;
  + Auer rods



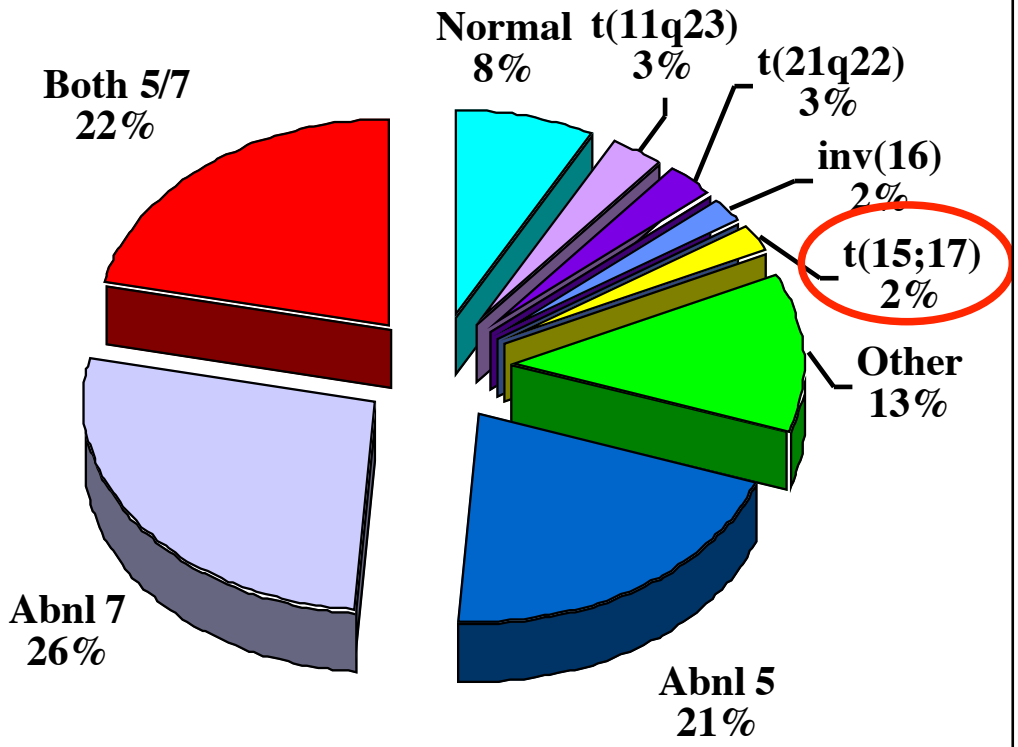
- 46XY,t(15;17)
- RT-PCR+ for *PML/RARA*, short isoform
- *FLT3*-wt; *NPM1*-wt
- Induction & consolidation with ATRA + ATO → CR
- Hematologic & molecular remission

Therapy-related Myeloid Neoplasm

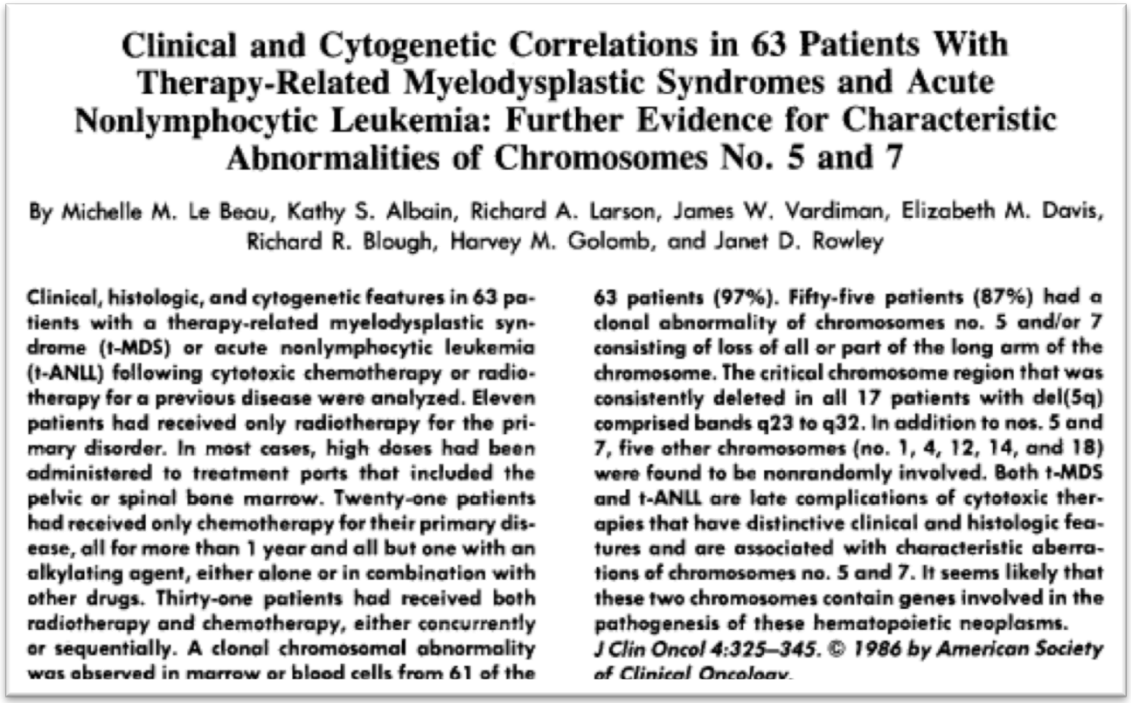
AML de novo



t-MDS/t-AML



University of Chicago Cytogenetics Laboratory



Clinical and Cytogenetic Correlations in 63 Patients With Therapy-Related Myelodysplastic Syndromes and Acute Nonlymphocytic Leukemia: Further Evidence for Characteristic Abnormalities of Chromosomes No. 5 and 7

By Michelle M. Le Beau, Kathy S. Albain, Richard A. Larson, James W. Vardiman, Elizabeth M. Davis, Richard R. Blough, Harvey M. Golomb, and Janet D. Rowley

Clinical, histologic, and cytogenetic features in 63 patients with a therapy-related myelodysplastic syndrome (t-MDS) or acute nonlymphocytic leukemia (t-ANLL) following cytotoxic chemotherapy or radiotherapy for a previous disease were analyzed. Eleven patients had received only radiotherapy for the primary disorder. In most cases, high doses had been administered to treatment ports that included the pelvic or spinal bone marrow. Twenty-one patients had received only chemotherapy for their primary disease, all for more than 1 year and all but one with an alkylating agent, either alone or in combination with other drugs. Thirty-one patients had received both radiotherapy and chemotherapy, either concurrently or sequentially. A clonal chromosomal abnormality was observed in marrow or blood cells from 61 of the 63 patients (97%). Fifty-five patients (87%) had a clonal abnormality of chromosomes no. 5 and/or 7 consisting of loss of all or part of the long arm of the chromosome. The critical chromosome region that was consistently deleted in all 17 patients with del(5q) comprised bands q23 to q32. In addition to nos. 5 and 7, five other chromosomes (no. 1, 4, 12, 14, and 18) were found to be nonrandomly involved. Both t-MDS and t-ANLL are late complications of cytotoxic therapies that have distinctive clinical and histologic features and are associated with characteristic aberrations of chromosomes no. 5 and 7. It seems likely that these two chromosomes contain genes involved in the pathogenesis of these hematopoietic neoplasms.

J Clin Oncol 4:325–345.

“ . . . two patients with a t(15;17) had the characteristic clinical and morphologic features of acute promyelocytic leukemia *de novo* and may reflect the development of acute leukemia unrelated to their prior cytotoxic therapies.”

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Le Beau et al. J Clin Oncol 1986; 4: 325

"Therapy-related" means leukemia that follows cytotoxic treatment with a DNA damaging agent.

- t-APL has been reported in cancer patients treated with:

  Topoisomerase II inhibitors

  Radiation therapy

  Alkylating agents

- t-APL has also been reported in patients who received chemotherapy for a non-malignant disorder.

(Post hoc, ergo propter hoc)

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Why identify cases as “therapy-related”?

- “Therapy-related” cases offer potential clues about the etiology of leukemia.
- These mechanisms may also apply to de novo disease.
- The label “therapy-related” does not by itself dictate how to manage the patient.
- Treatment should be based on cytogenetic characteristics and other clinical and biological risk factors.

Therapy-Related Acute Promyelocytic Leukemia

By M. Beaumont, M. Sanz, P.M. Carli, F. Maloisel, X. Thomas, L. Detourmignies, A. Guerci, N. Gratecos, C. Rayon, J. San Miguel, J. Odriozola, J.Y. Cahn, F. Huguet, A. Vekhof, A. Stamatoulas, H. Dombret, F. Capote, J. Esteve, A.M. Stoppa, and P. Fenaux

Purpose: To analyze patient cases of therapy-related acute promyelocytic leukemia (tAPL), occurring after chemotherapy (CT), radiotherapy (RT) or both for a prior disorder, diagnosed during the last 20 years in three European countries.

Patients and Methods: The primary disorder and its treatment, interval from primary disorder to tAPL, characteristics of tAPL, and its outcome were analyzed in 106 patients.

Results: Eighty of the 106 cases of tAPL were diagnosed during the last 10 years, indicating an increasing incidence of tAPL. Primary disorders were predominantly breast carcinoma (60 patients), non-Hodgkin's lymphoma (15 patients), and other solid tumors (25 patients). Thirty patients had received CT alone, 27 patients had received RT alone, and 49 patients had received both. CT included at least one alkylating agent in 68 patients and at least one topoisomerase II inhibitor in 61 patients, including anthracyclines (30 patients), mitoxantrone (28 patients), and epipodophyllotoxins (19 patients). Median interval from primary disorder to tAPL diagnosis was 25 months (range, 4 to 276 months). Characteristics of tAPL were generally similar to those of de novo APL. With treatment using anthracycline-cytarabine-based CT or all-*trans*-retinoic acid combined with CT, actuarial survival was 59% at 8 years.

Conclusion: tAPL is not exceptional, and develops usually less than 3 years after a primary neoplasm (especially breast carcinoma) treated in particular with topoisomerase II–targeted drugs (anthracyclines or mitoxantrone and less often etoposide). Characteristics and outcome of tAPL seem similar to those of de novo APL.

J Clin Oncol 21:2123-2137.

"... Characteristics and outcome of t-APL seem similar to those of *de novo* APL. ..."

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Beaumont et al. J Clin Oncol 2003; 21: 2123

Is the incidence of t-APL increasing?

- University Hospital of Lille, France

  Proportion of all APL that was therapy-related:

1984-1993	5%
1994-2000	22%

- MD Anderson Cancer Center, Houston, Texas

1986	1	t-APL among 60 patients with APL (2%)
1996	14	t-APL among 113 patients with APL (12%)

International Workshop on the Relationship of Prior Therapy to Balanced Chromosome Aberrations in Therapy-Related Myeloid Leukemia

(MK Andersen et al. Genes Chromos Cancer 2002; 33: 395-400)

		t(15;17) N=41
Male : female		15 : 26
Age at primary diagnosis: median (range), years		46 (18-79)
Cytotoxic exposure:		
Radiation only		12 (29%)
Chemotherapy only		7 (17%)
Combined RT + chemo		22 (54%)
Age at t-MN: median (range)		49 (19-81)
Latency from first treatment: Median (range), months		29 (9-175)

International Workshop on the Relationship of Prior Therapy to Balanced Chromosome Aberrations in Therapy-Related Myeloid Leukemia

(MK Andersen et al. Genes Chromos Cancer 2002; 33: 395-400)

	inv(16) N=48	t(15;17) N=41
Male : female	18 : 30	15 : 26
Age at primary diagnosis: median (range), years	43 (6-75)	46 (18-79)
Cytotoxic exposure:		
Radiation only	10 (21%)	12 (29%)
Chemotherapy only	14 (29%)	7 (17%)
Combined RT + chemo	24 (50%)	22 (54%)
Age at t-MN: median (range)	48 (13-77)	49 (19-81)
Latency from first treatment: Median (range), months	22 (8-533)	29 (9-175)

International Workshop on the Relationship of Prior Therapy to Balanced Chromosome Aberrations in Therapy-Related Myeloid Leukemia

(MK Andersen et al. Genes Chromos Cancer 2002; 33: 395-400)

Primary diagnoses	inv(16) N=48	t(15;17) N=41
Hodgkin lymphoma	8 (17%)	4 (10%)
Non-Hodgkin lymphoma	4 (8%)	7 (17%)
Breast cancer	15 (31%)	18 (44%)
Testicular cancer	1 (2%)	3 (7%)
Uterine cancer	1 (2%)	2 (5%)
Lung cancer	2 (4%)	1 (2%)
Other solid tumors	10 (21%	5 (12%)
Sarcoma	5 (10%)	-
Nonmalignant	1 (2%)	1 (2%)

Therapy-related Acute Promyelocytic Leukemia

Primary diagnoses	France, Spain, Belgium N=106	Literature reports N=324
Hodgkin lymphoma	2 (2%)	16 (5%)
Non-Hodgkin lymphoma	15 (14%)	27 (8%)
Breast cancer	60 (57%)	97 (30%)
Testicular cancer	-	44 (14%)
Uterine cancer	4 (4%)	
Lung cancer	1 (1%)	6 (2%)
Other solid tumors	20 (19%)	35 (11%)
Nonmalignant	2 (2%)	80 (25%)

Beaumont et al. J Clin Oncol 2003; 21: 2123;
Rashidi & Fisher. Med Oncol 2013; 30: 625

Therapy-related Acute Promyelocytic Leukemia

	France, Spain, Belgium N=106	**Literature reports N=287**	International Workshop N=41	***de novo* APL**
Median Latency, months (range)	**25 (4-276)**	**24 (IQR,16-41)**	**29 (9-175)**	**N/A**
Secondary cytogenetic rearrangements	**25%**	**46%**	**41%**	**26%**
Abnormal No. 5, 7, or 17	**17%**		**7%**	**3%**
Trisomy 8	**5%**	**7%**	**12%**	**12%**

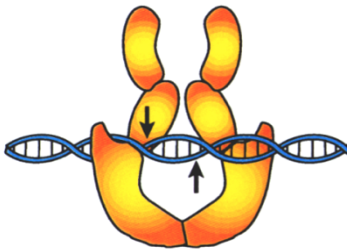
Beaumont et al. J Clin Oncol 2003; 21: 2123
Rashidi & Fisher. Med Oncol 2013; 30: 625 (N=326)
Andersen et al. Genes Chromos Cancer 2002; 33: 395.

N/A, not applicable

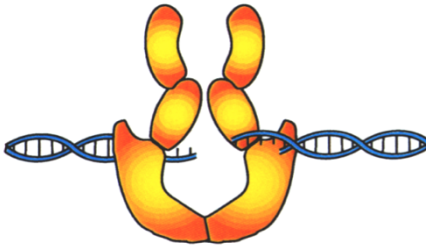
t-APL after mitoxantrone treatment for multiple sclerosis

- Mitoxantrone -- an anthracenedione commonly used in breast cancer, lymphoma, AML
  - topoisomerase II inhibitor
  - immunosuppressive
  - use in multiple sclerosis began in the mid-1990's
- By 2002, several cases of t-AML had been reported
  - Ghalie et al. Multiple Sclerosis 2002; 8: 441
- In 2008, the 8th and 9th cases of t-APL were reported
  - Ramkumar et al. Cancer Genet Cytogen 2008; 182: 126
- In 2008, 14 more cases of t-APL
  - Hasan et al. BLOOD 2008; 112: 3383

Topoisomerase II: Life and Death



Cleavage ⇅ *Religation*



Topoisomerase II-DNA
Cleavage Complex

Normal Cell Growth

Control of DNA Topology

Proper Chromosome Segregation

Recombination
Mutagenesis
Translocations

Apoptosis

Anticancer Drugs

CELL DEATH

Drugs
Toxins
Natural Products

DNA Translocations
CANCER

***MLL* (11q23)**
PML-RARA t(15;17)

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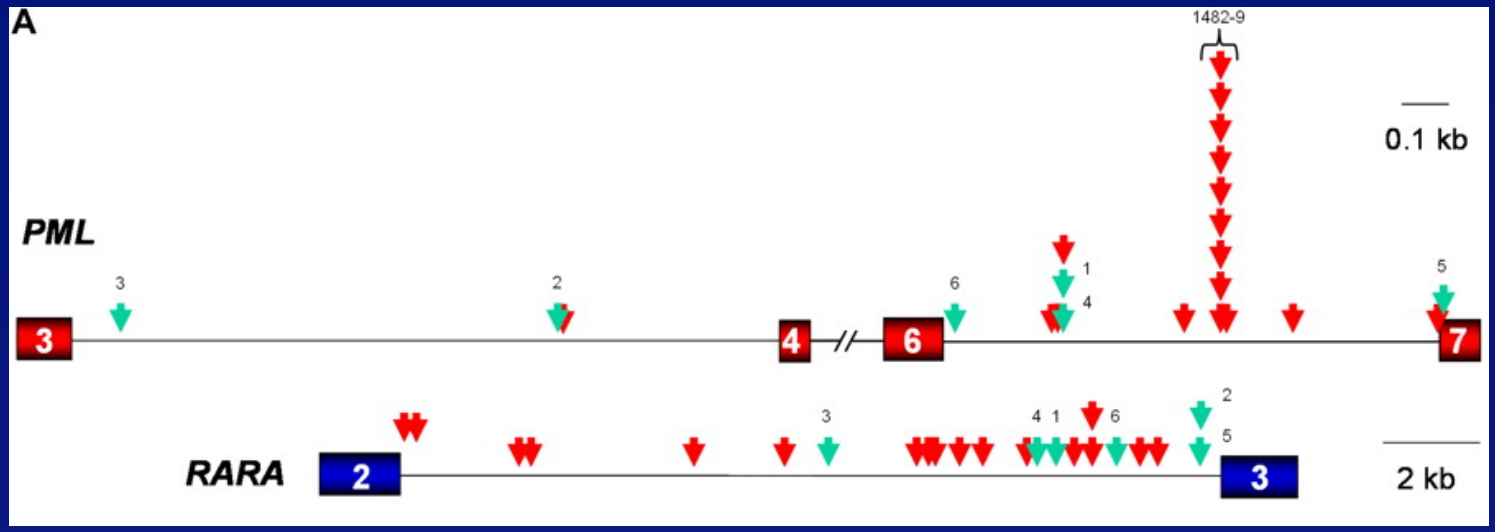
Courtesy of Neil Osheroff

“Hot spots” of DNA damage from epirubicin and mitoxantrone



- Chromosomal breakpoints cluster at strong topoisomerase II-DNA cleavage sites that are different for mitoxantrone and epirubicin.
  - **Green arrows – epirubicin**
  - **Red arrows -- mitoxantrone**
- APL with the same breakpoints for t(15:17) are found in multiple sclerosis patients treated with mitoxantrone.

Mays et al. Blood 2010; 115: 326

Factors that affect the outcome of patients with t- APL

- Persistence of the primary malignant disease
- Prior treatment injury to organs and vascular supply
- Depletion of normal hematopoietic stem cells
- Damage to bone marrow stroma (myelofibrosis)
- Chronic immunosuppression (dysfunctional phagocytes)
- Colonization with pathogenic bacteria and fungi
- Refractoriness to transfusion support

Conclusions – characteristic features of t-APL

- Median age ~ 47 years; F > M
- Short latency ~ 2-3 years
- Topoisomerase-II inhibitors or radiation therapy
- Breast cancer, hematologic malignancies, multiple sclerosis, GU
- Morphology and clinical course is same as *de novo* APL.
- Rarely have dysplasia or preleukemic phase.
- t(15;17) is the sole cytogenetic abnormality in most patients.
- More often have additional chromosomal abnormalities.
- Different DNA damage “hot spots” depending upon agent
- *FLT3* mutations are common; *IDH* and *TET2* mutations are rare.
- Excellent response to ATRA + arsenic trioxide

Questions to be considered

- Do t-APL patients harbor germline mutations in predisposition genes?
  - Or polymorphisms in DNA repair mechanisms?
  - Probably do not have underlying clonal hematopoiesis.
- Is a “second hit” necessary after the *PML/RARA* fusion gene forms, or is a single transforming event sufficient?
- Does prior chemotherapy suppress immune surveillance that otherwise would eradicate preleukemic stem cells with *PML/RARA*?

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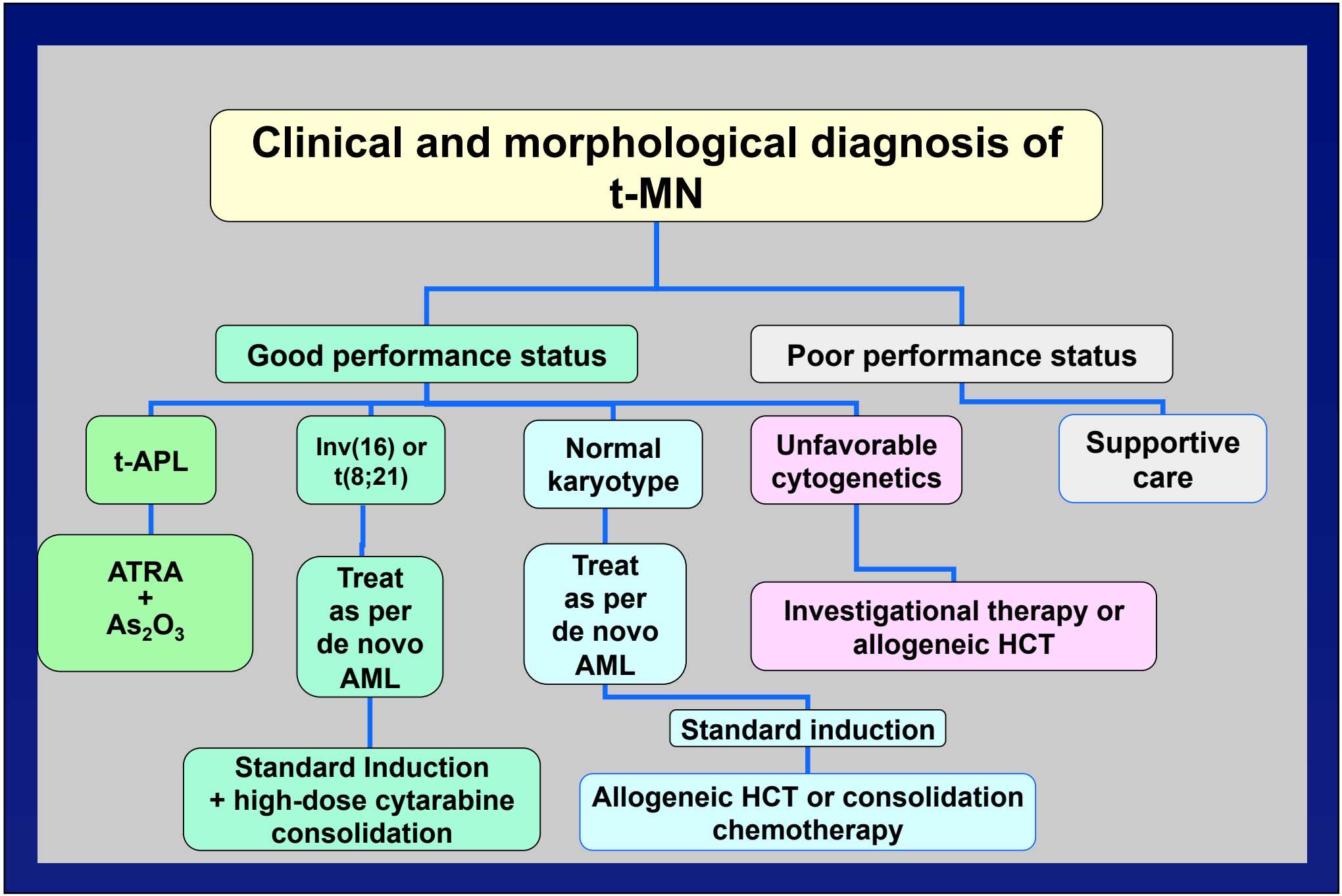
Clinical and morphological diagnosis of t-MN
Good performance status
Poor performance status
t-APL
Inv(16) or t(8;21)
Normal karyotype
Unfavorable cytogenetics
Supportive care
ATRA + As_2O_3
Treat as per de novo AML
Treat as per de novo AML
Investigational therapy or allogeneic HCT
Standard induction
Standard Induction + high-dose cytarabine consolidation
Allogeneic HCT or consolidation chemotherapy