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!
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AUER RODS STINK!
TYPICALLY AFFECTS ADULTS GREATER THAN 65 YEARS OF AGE
LEUKOSTASIS, CNS SYMPTOMS, DISSEMINATED INTRAVASCULAR COAGULATION (DIC)
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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*

AML with myelodysplasia-related changes

Therapy-related myeloid neoplasms

AML, not otherwise specified

- AML with minimal differentiation
- AML without maturation
- AML with maturation
- Acute myelomonocytic leukemia
- Acute monoblastic/monocytic 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

Swerdlow SH, Campo E, Harris NL, et al (eds): WHO classification of tumours of haematopoietic and lymphoid tissues. Lyon, France: IARC Press; 109–138, 2009.

Vardiman JW, Thiele J, Arber DA, et al: The 2008 revision of the World Health Organization classification of myeloid neoplasms and acute leukemia: Rationale and important changes. Blood 114:937–951, 2009

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

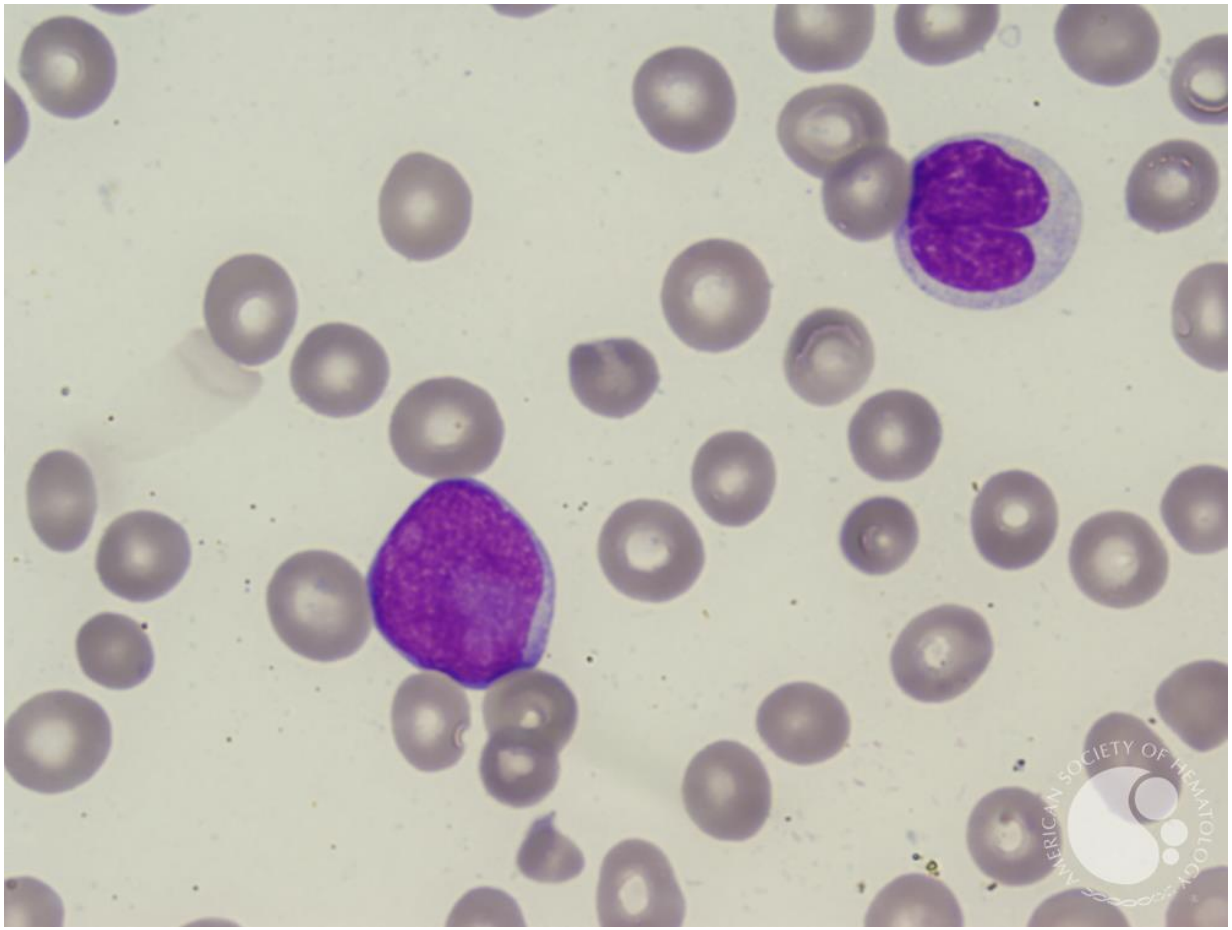
Description:

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 rearrangment 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

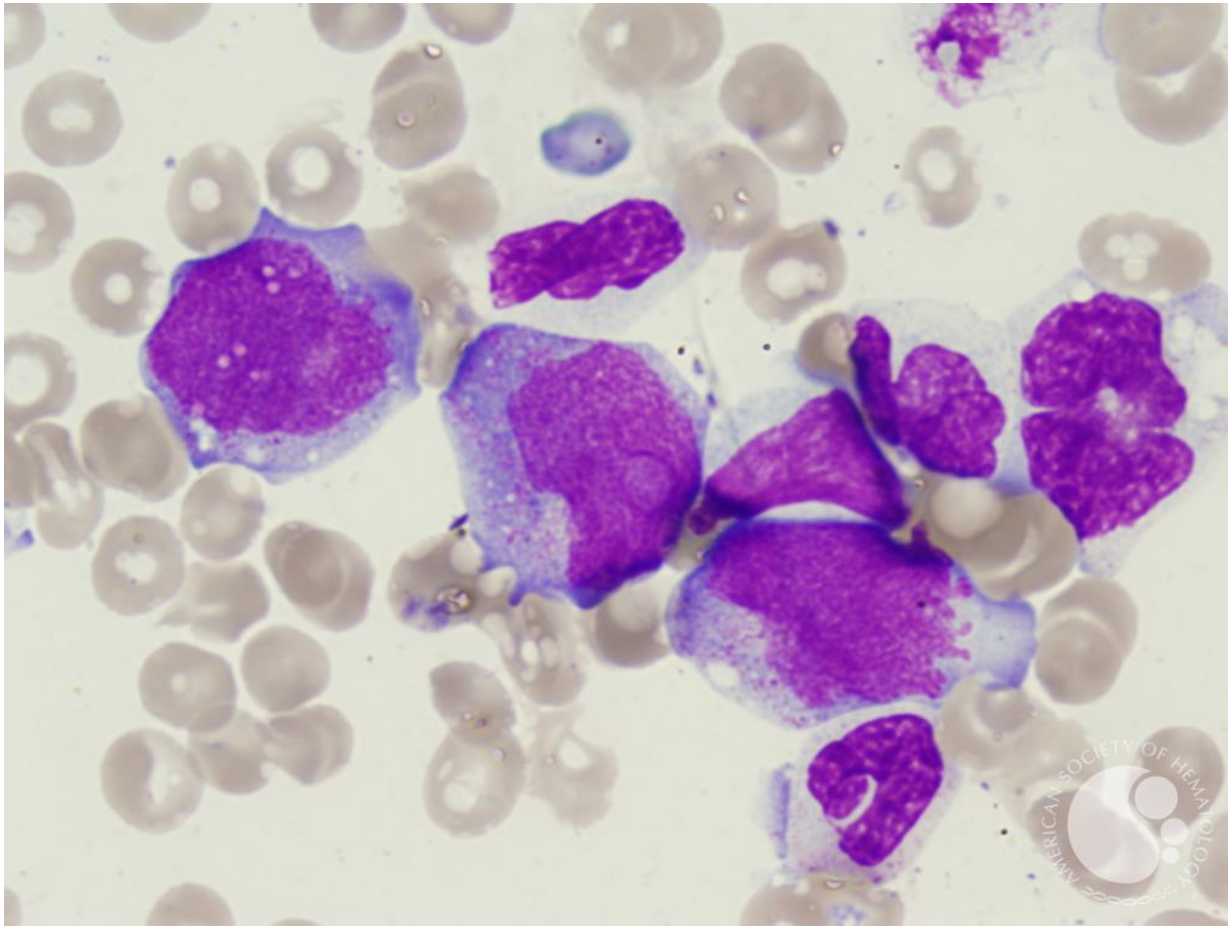
The peripheral blood shows anemia, thrombocytopenia, and a leukocytosis with numerous circulating blasts.



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)

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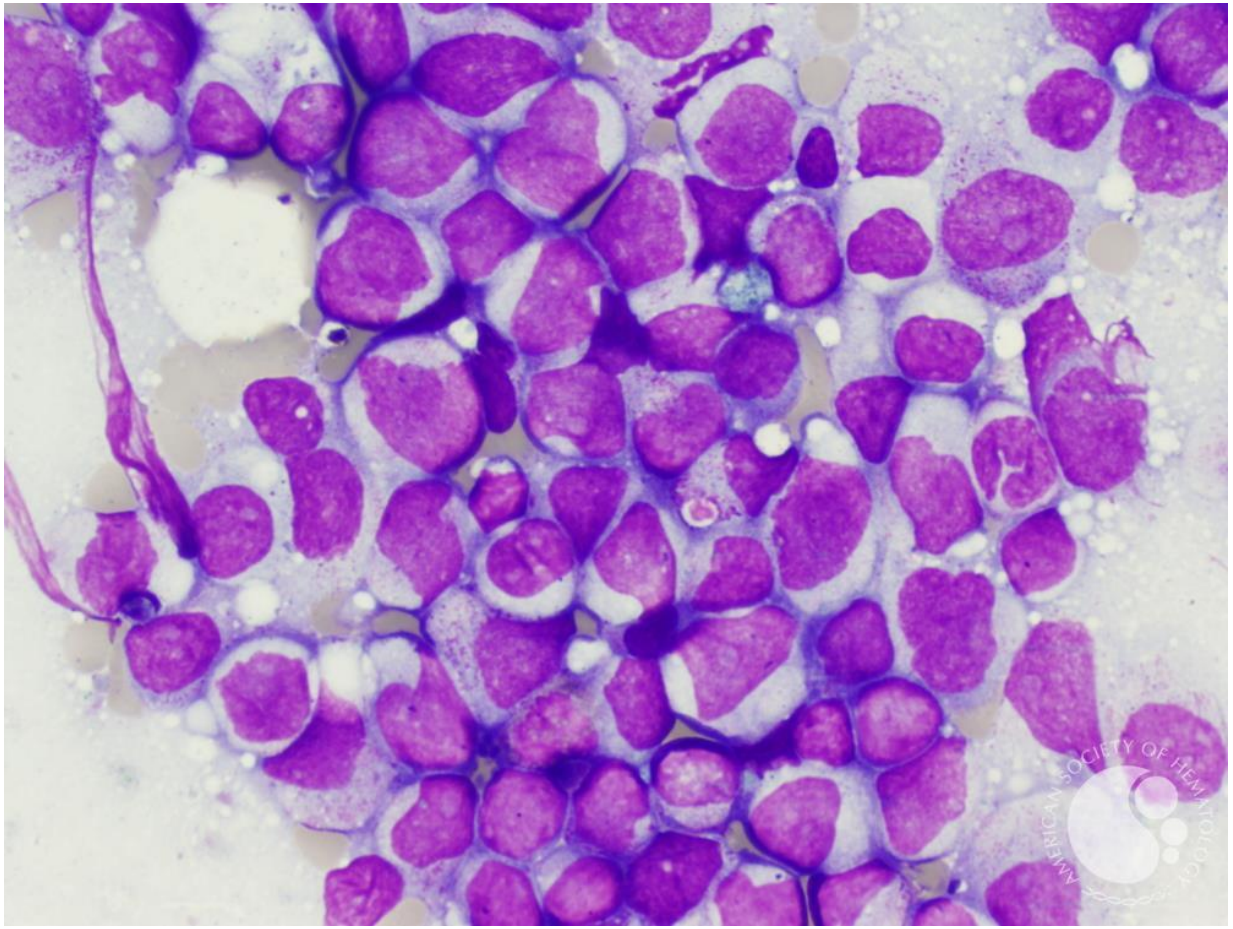
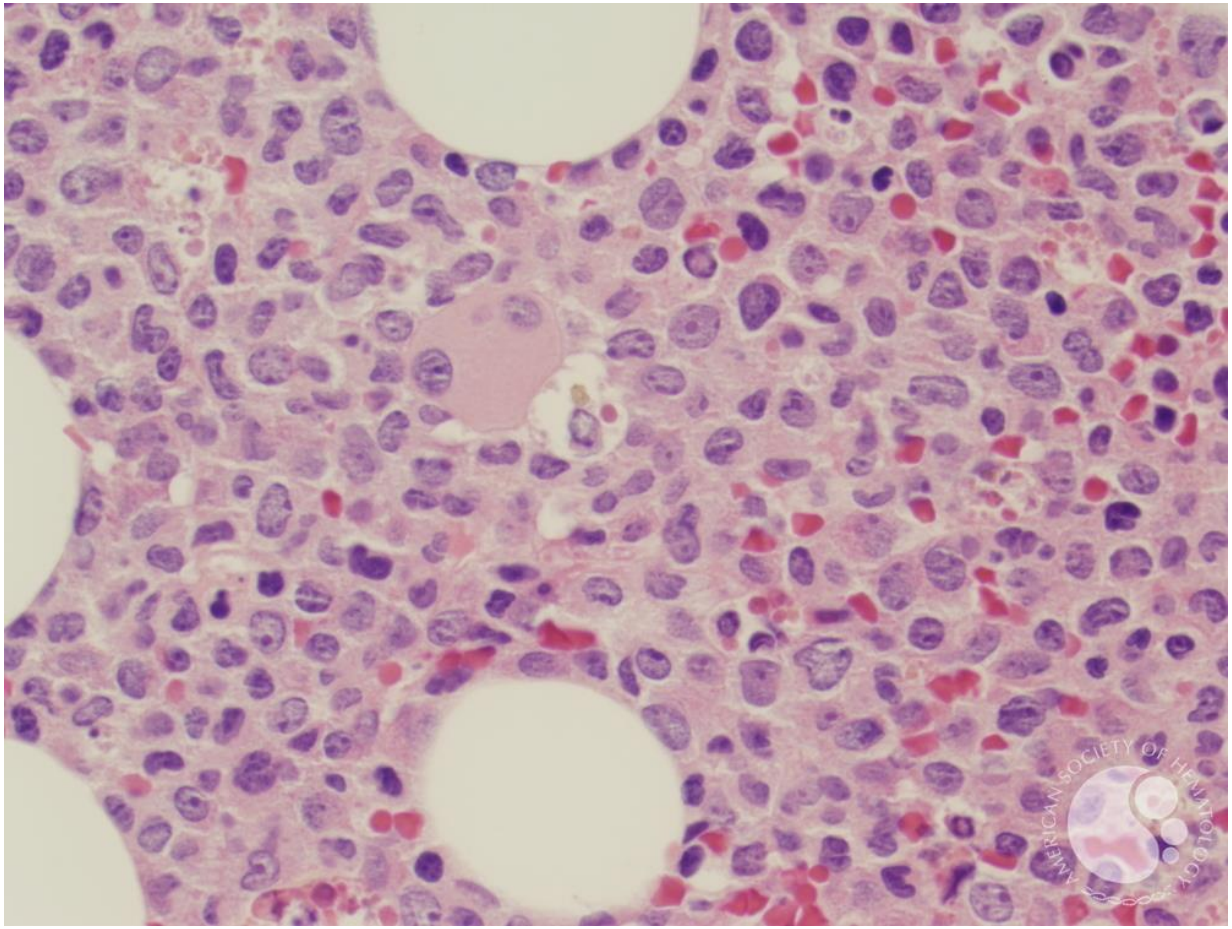


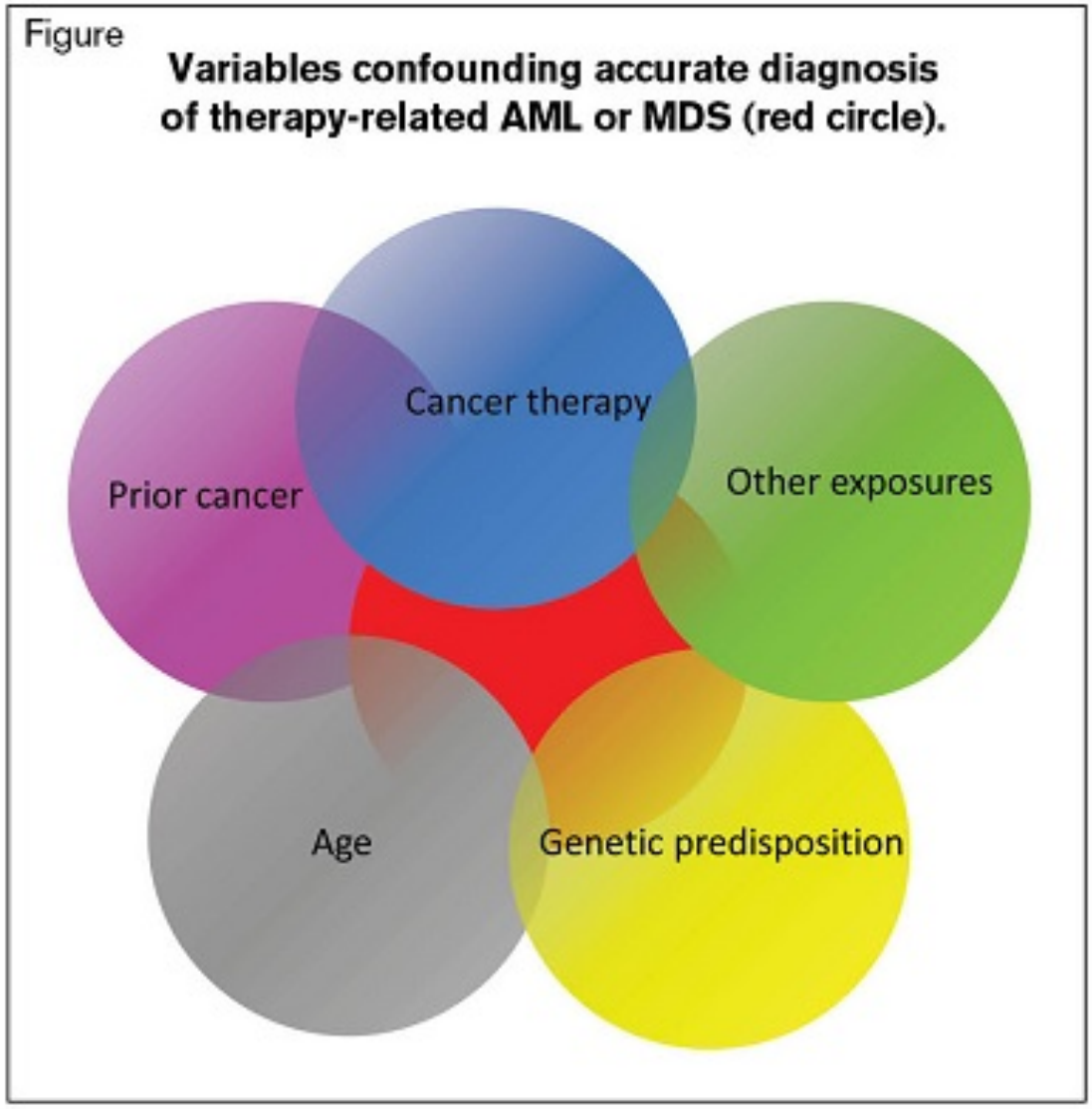
Therapy-related myeloid neoplasm (Acute myeloid leukemia)

Trephine Core

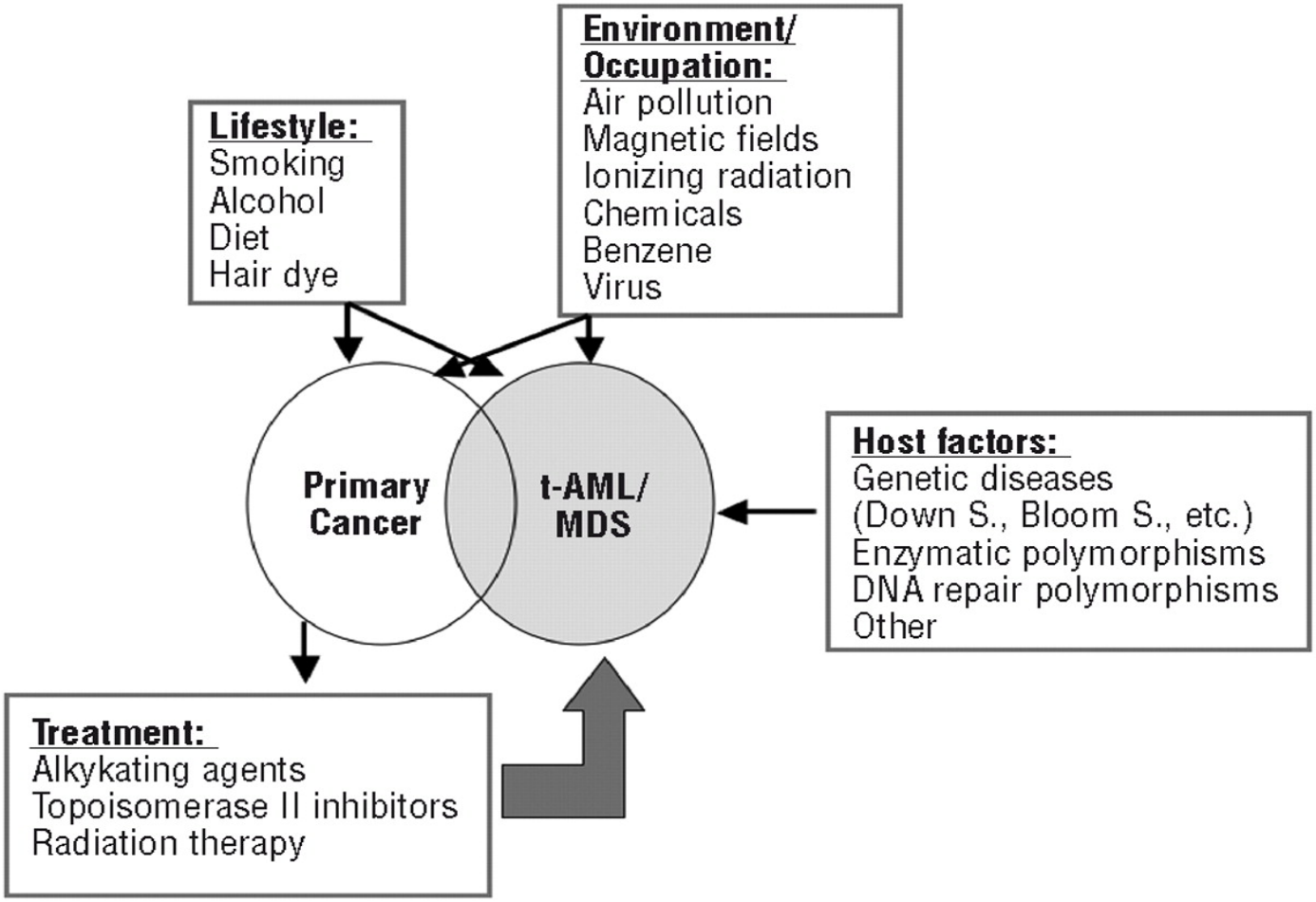
The trephine core is hypercellular with frequent blasts. Scattered megakaryocytes are notable for widely separated nuclear lobes.



Risk factors for therapy-related AML/MDS



Risk factors for therapy-related AML/MDS



Giuseppe Leone et al. Haematologica 2007;92:1389-1398

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

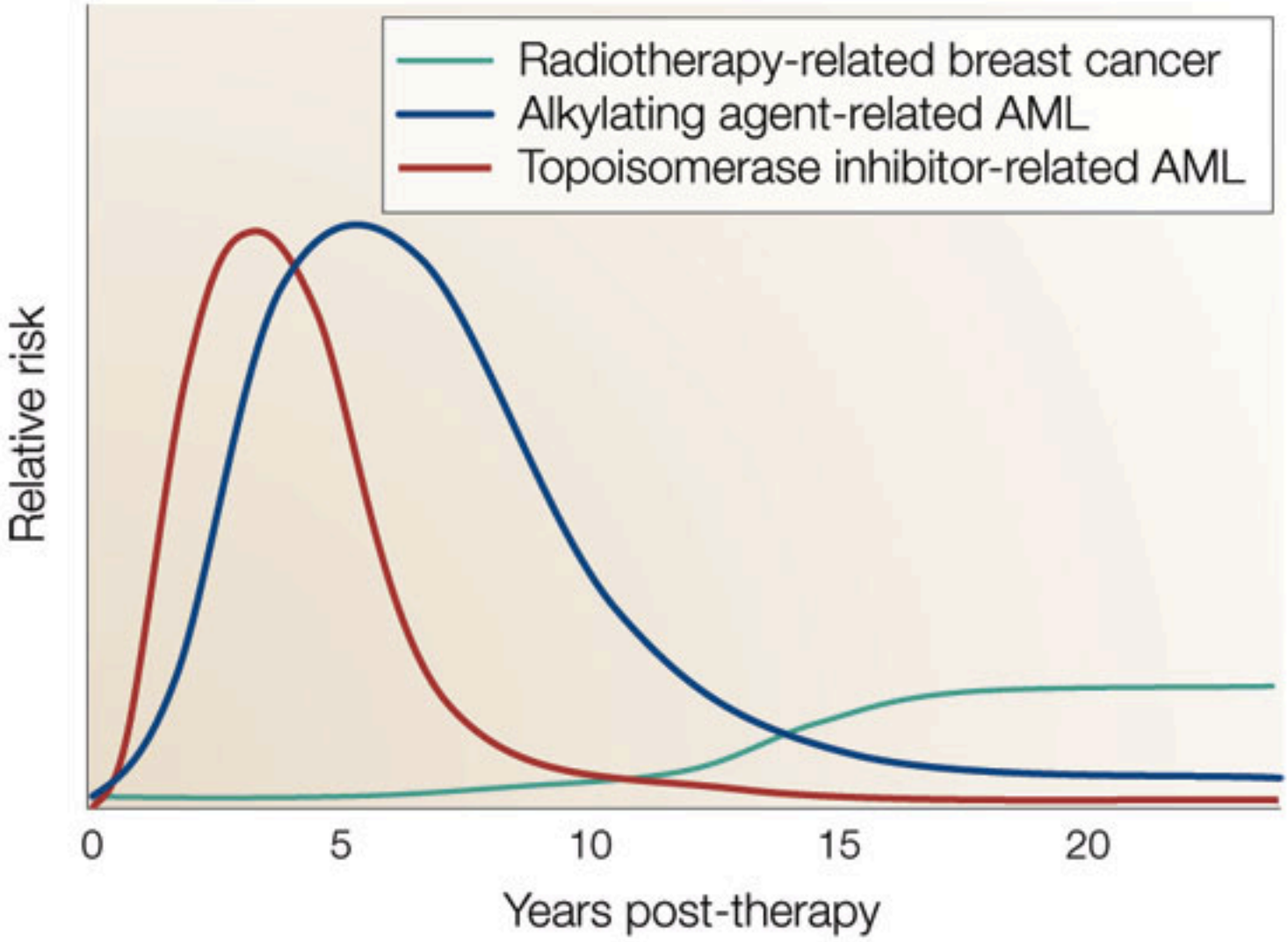
Table 1.

Anti-cancer agents and detoxification/DNA repair.

Table 1. Anti-cancer agents and detoxification/DNA repair.

Class		*GST*	*CYP*	*DNA repair*
Alkylating agents	Mechlorethamine Cyclophosphamide Melphalan Busulphan BCNU, CCNU	GSTT1 GSTM1 GSTP1	CYP2B6 CYP2C19 CYP3A4	MGMT BER (RAD51 XRCC3)
Topoisomerase I inhibitors	Topotecan Irinotecan		CYP3A	NHEJ
Topoisomerase II inhibitors	Mitoxantrone Daunorubicin Doxorubicin Etoposide Teniposide	(GSTP1)	CYP1B1 CYP3A4	NHEJ (RAD51 XRCC3)
Ionizing radiation				(RAD51 XRCC3)

Leone G, et al, Haematologica 2007;92(10):1389-98.



Nature Reviews | Cancer

Risk factors for t-AML/MDS after Rx for Hodgkin lymphoma

Table 2.

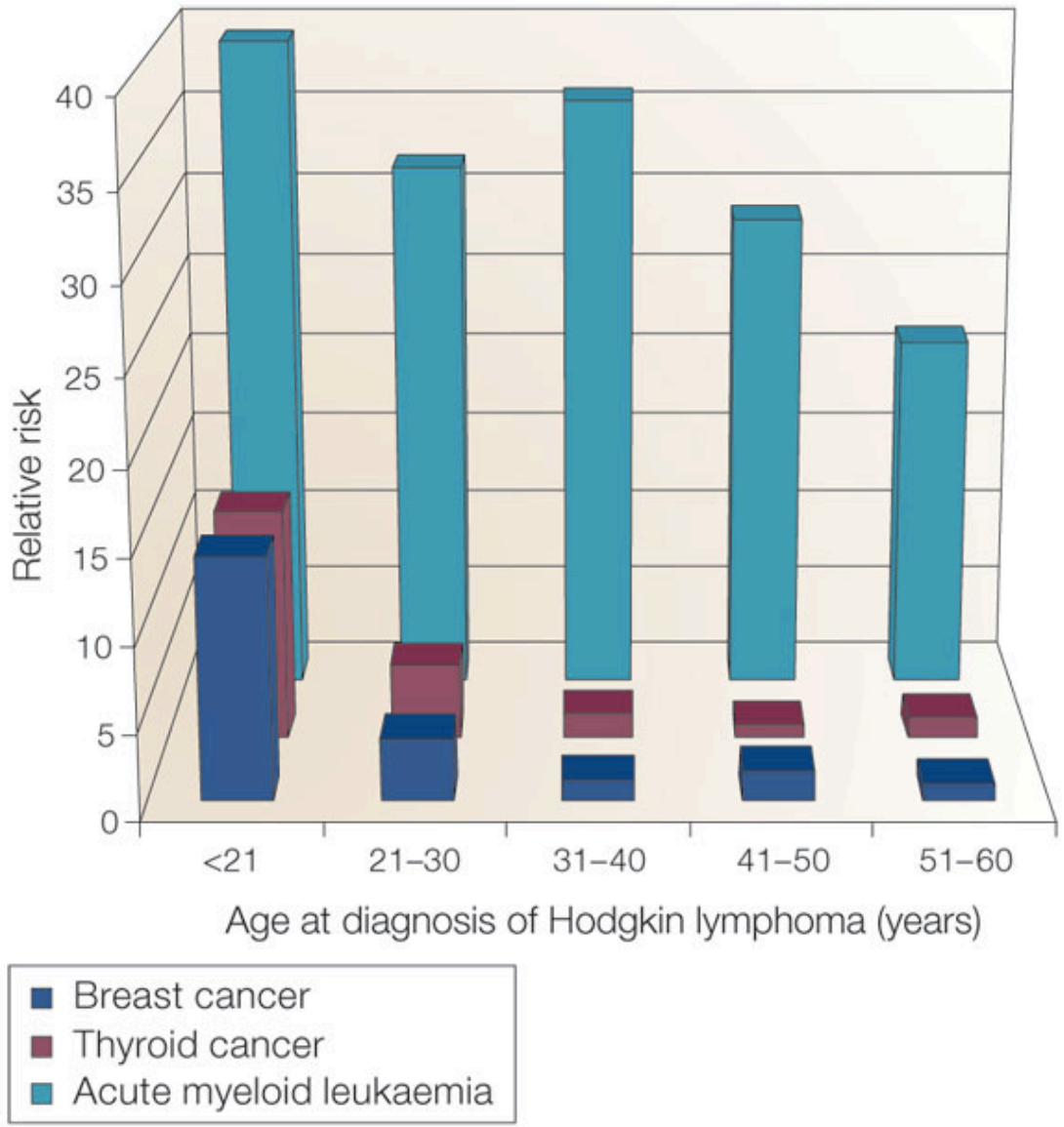
Risk of MDS/AML in patients receiving chemo/radiotherapy for Hodgkin's lymphoma, according to treatment.

Table 2. Risk of MDS/AML in patients receiving chemo/radiotherapy for Hodgkin's lymphoma, according to treatment.

References	*No. of pts*	*Therapy*	*Cases of t-MDS/AML*	*Cumulative Risk (%)*
Brusamolino *et al.*[35]	348	RT	2	0.3
Josting *et al.*[37]	677		4	0.6
Brusamolino *et al.*[35]	124	MOPP	3	2.2
Josting *et al.*[37]	1775	COPP+ABVD	15	0.8
Brusamolino *et al.*[35]	277	MOPP+RT	18	10.2 (15 yrs)
Delwail *et al.*[36]	374	(involved field)	5	2.4 (15 yrs)
Delwail *et al.*[36]	36	(extended field)	4	13.9 (15 yrs)
Brusamolino *et al.*[35]	24	ABVD	0	0
Josting *et al.*[37]	304		1	0.3
Brusamolino *et al.*[35]	129	ABVD+RT	1	0.8
Delwail *et al.*[36]	279	(involved field)	2+1 (ALL)	1.2
Delwail *et al.*[36]		(extended field)	0	0
Josting *et al.*[37]	500	BEACOPP baseline	2	0.4
	460	BEACOPP escalated	8	1.7

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

Leone G, et al, Haematologica 2007;92(10):1389-98.



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

Table 3.

Incidence and relative risk of t-MDS-AML in breast cancer. Distribution of leukemia cases by treatment.

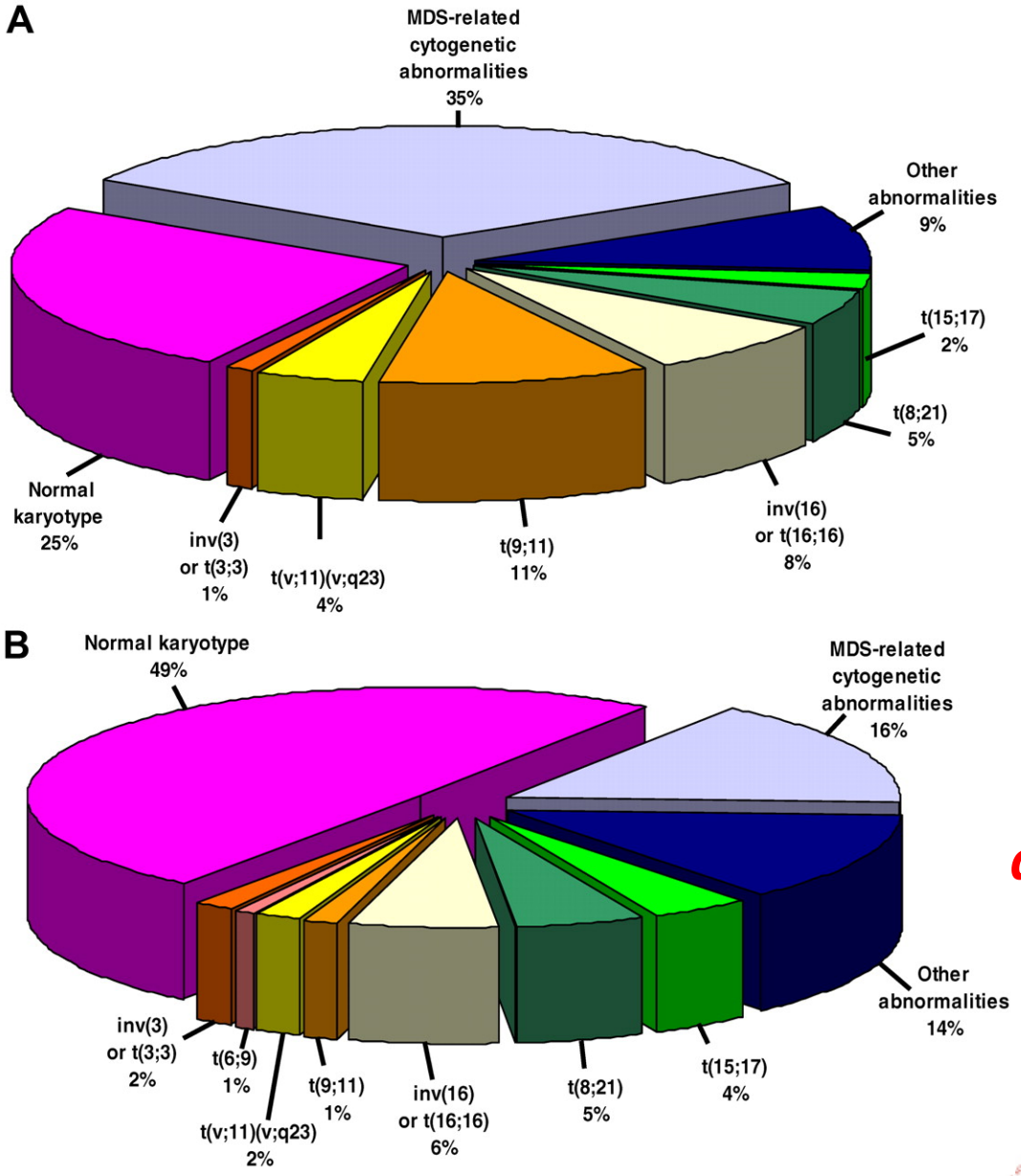
Table 3. Incidence and relative risk of t-MDS-AML in breast cancer. Distribution of leukemia cases by treatment.

References	No. of pts.	Therapy	Cases of t-MDS/AML (No.)	Cumulative risk (%)
Praga *et al.*[64]	7110	Epirubicin regimens	28	0.55 (8 y)
	1427	CMF	1	0.07
	903	Hormone therapy	1	0.11
Smith *et al.*[60]	4483	B15-Doxorubicin +CTX (2400 mg/m^2)	11	0.27 (8 y)
	763	B16-Doxorubicin +CTX (4800 mg/m^2)	4	0.40 (8 y)
	772	B18-Doxorubicin +CTX (4800 mg/m^2)	6	0.52 (8 y)
	849	B22-Doxorubicin +CTX (4800 mg/m^2)	4	0.47 (8 y)
	847	B23-Doxorubicin +CTX (4800 mg/m^2)	10	1.19 (8 y)
	849	B25-Doxorubicin +CTX (9600 mg/m^2)-G-CSF	8	0.95 (8 y)
Hershman *et al.*[66]	1569	Doxorubicin regimens	18	1.14
	3330	CTX regimen	40	1.20
	2837	Radiotherapy	38	1.33
	890	G-CSF/GM-CSF treatment*	16	1.79
Kapplan[67]	154	Surgery only	1/2**	0.65/1.30**
	1403	Surgery + Radiotherapy	0/4**	0/0.29**
	352	Surgery + Chemotherapy	0/0**	0/0**
	957	Surgery + Chemotherapy + Radiotherapy	2/2**	0.21/0.21**
Howard *et al.*[68]	89560	Surgery only	133**	0.14**
	99275	Radiotherapy, no chemotherapy	221**	0.22**
	11941	Chemotherapy, no radiotherapy	14**	0.11**
	15130	Chemotherapy and radiotherapy	14**	0.09**

*The distribution of leukemia cases by treatment. CMF: cyclophosphamide (CTX), methotrexate, and fluorouracil; *p value: 0.06, compared to patients who did not receive G-CSF/GM-CSF; **all cases of leukemia (CML, AML and ALL) were included.*

Leone G, et al, Haematologica 2007;92(10):1389-98.

Distribution of cytogenetic abnormalities in t-AML



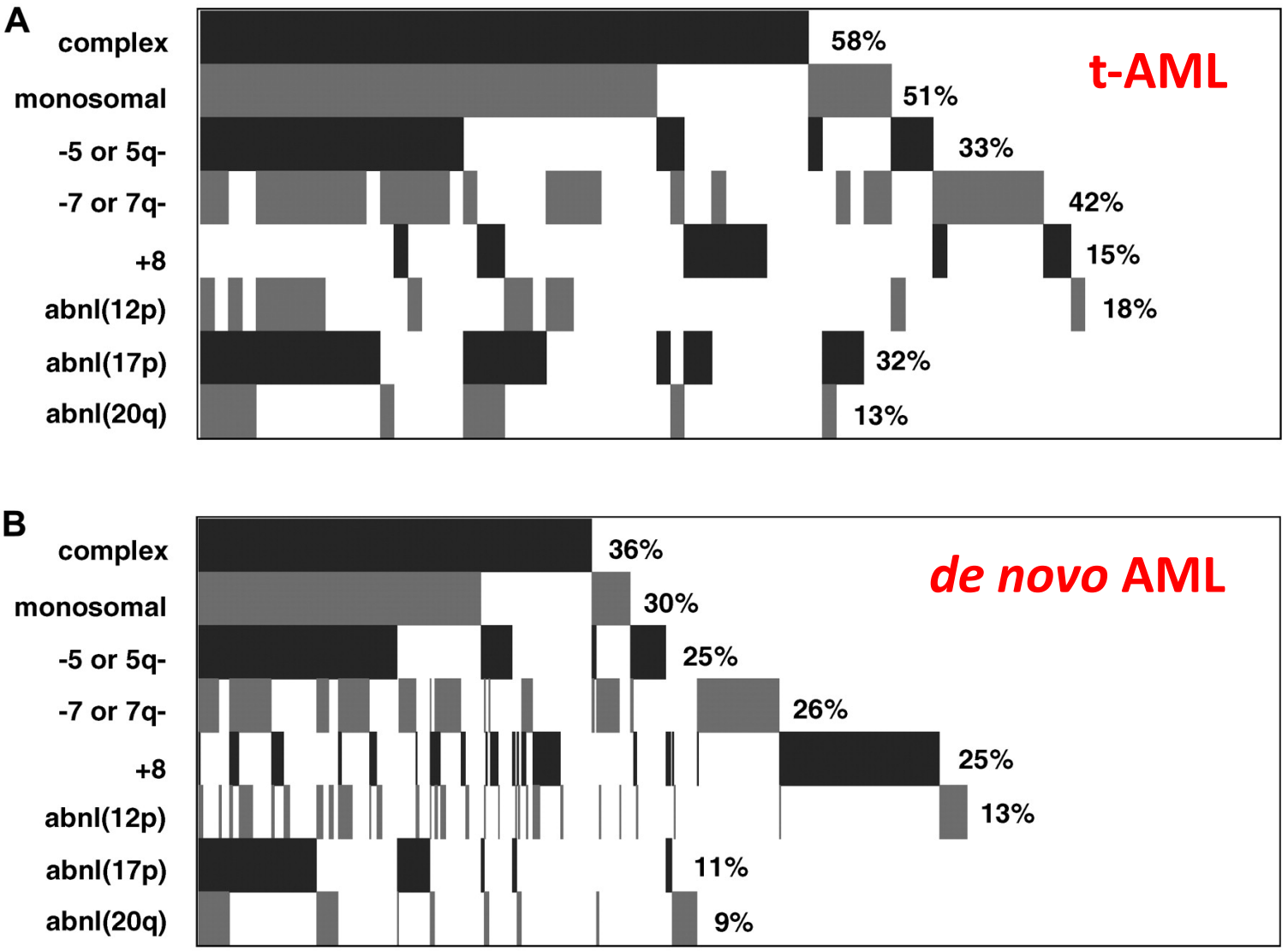
t-AML

***de novo* AML**

Sabine Kayser et al. Blood 2011;117:2137-2145

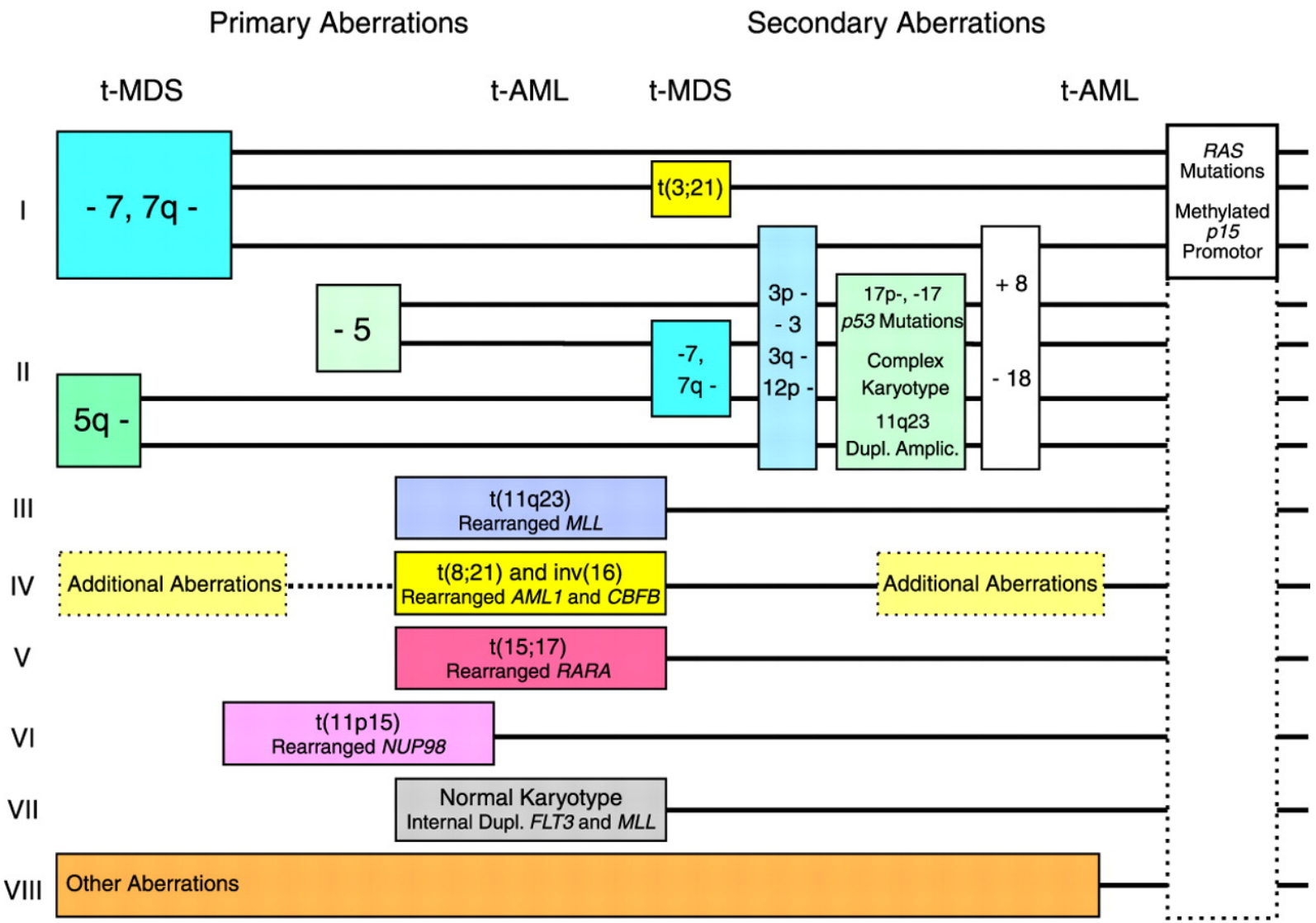
blood

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



Sabine Kayser et al. Blood 2011;117:2137-2145

Different genetic pathways in t-MDS and t-AML



Jens Pedersen-Bjergaard et al. Blood 2002;99:1909-1912

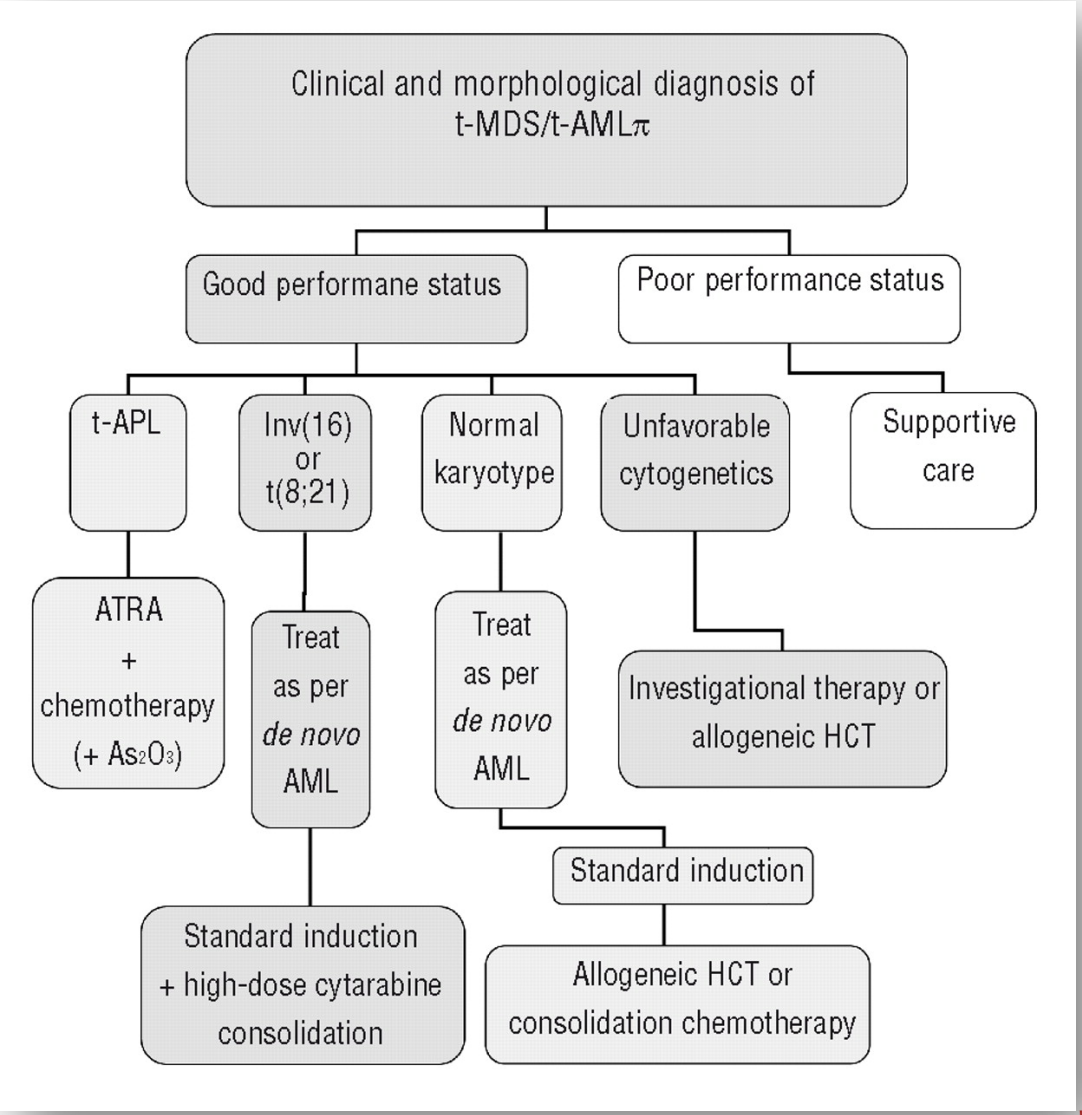
Treatment of t-AML

- 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



Richard A. Larson Haematologica 2009;94:454-459

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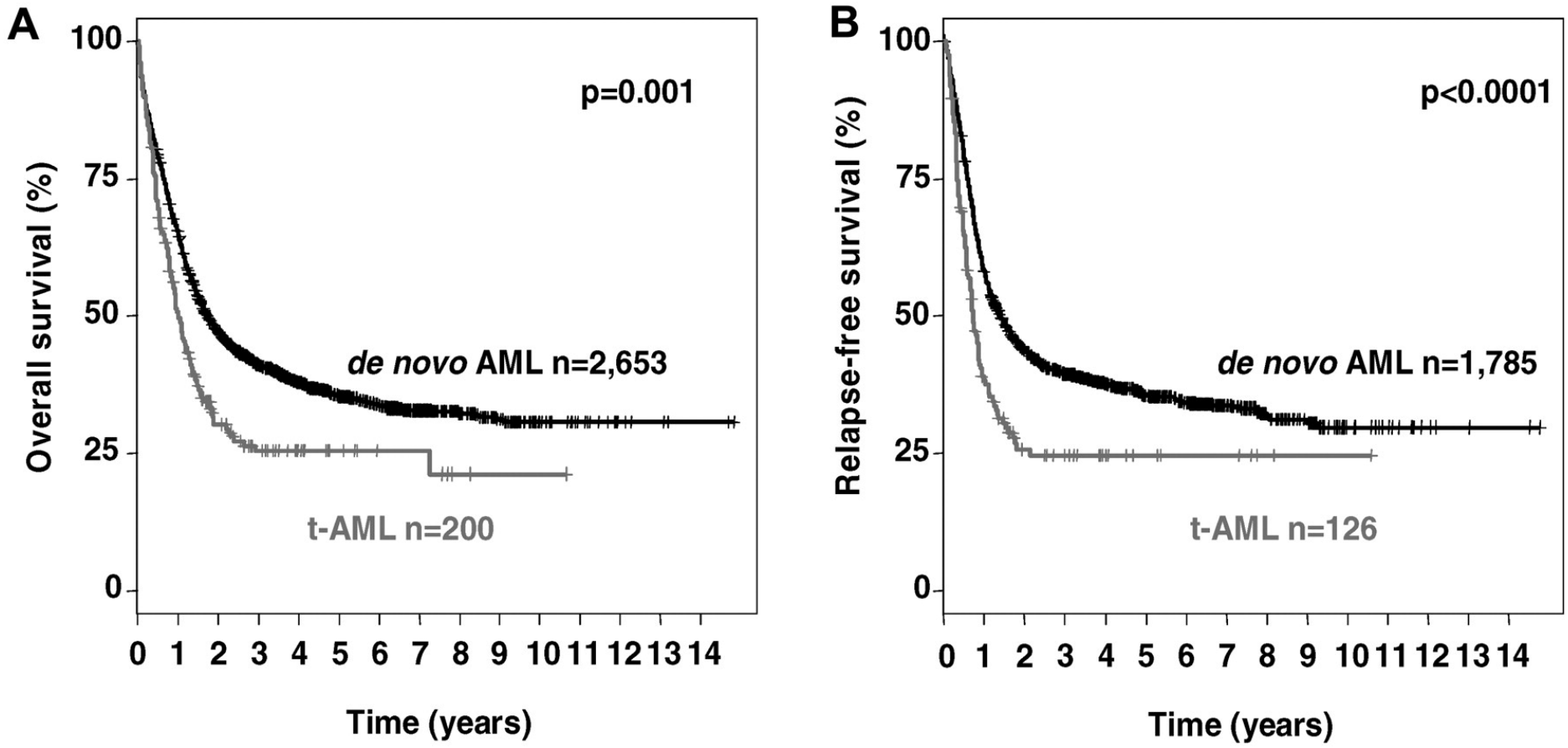
Kaplan-Meier survival analysis of overall and relapse-free survival in 2853 patients with de novo AML or t-AML



Sabine Kayser et al. Blood 2011;117:2137-2145

Kaplan-Meier survival analysis of 65 consecutive patients with t-AML after allogeneic transplantation

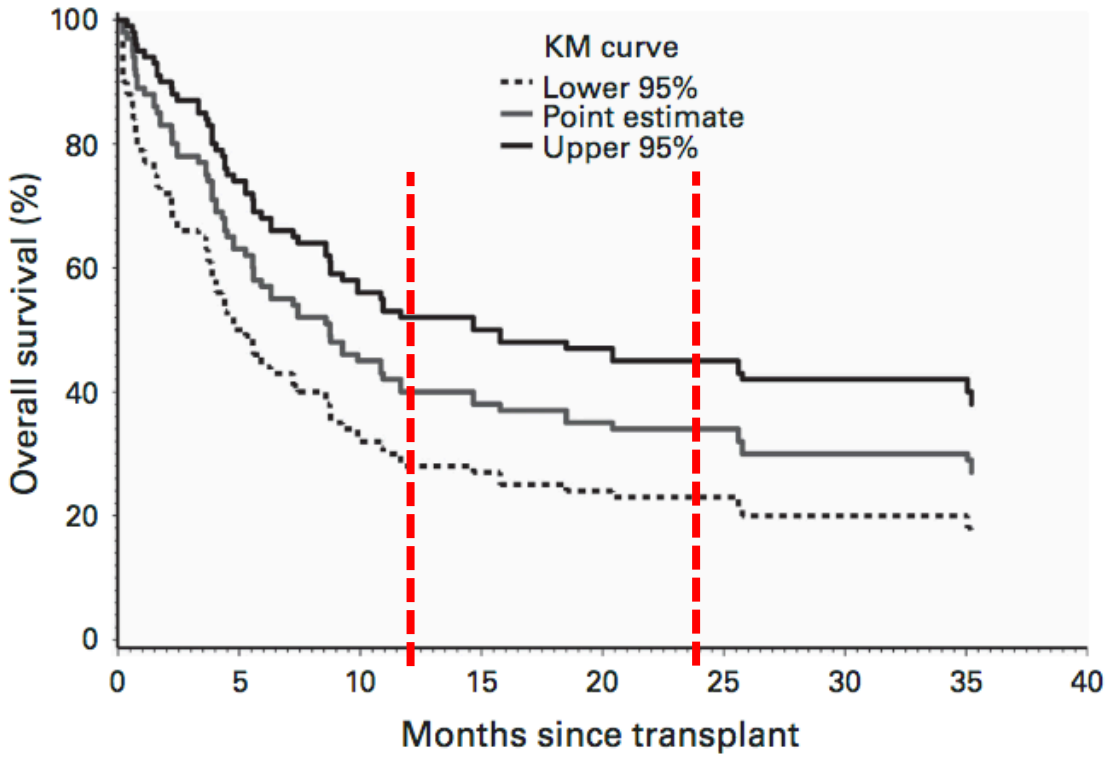
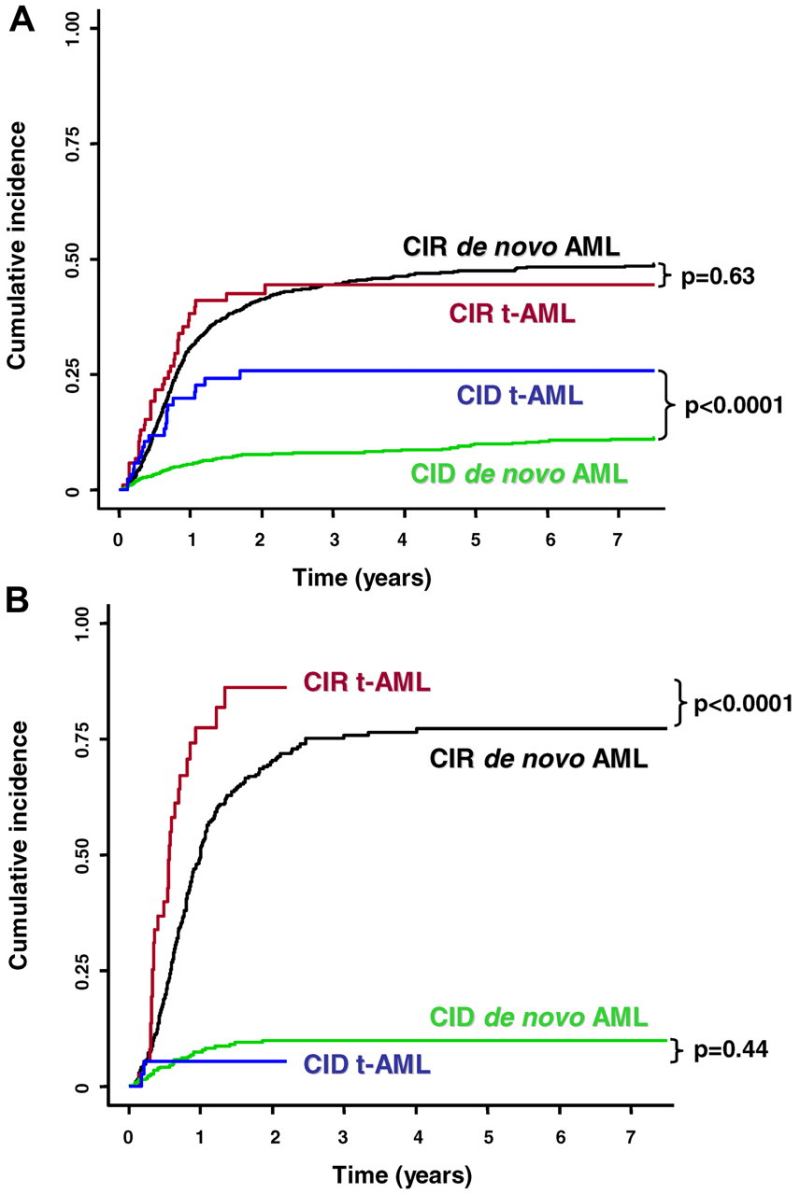


Figure 1. OS of all patients with t-AML/MDS.

Alam N, *et al*. Bone Marrow Transplantation 2015;50(9):1180-6.

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



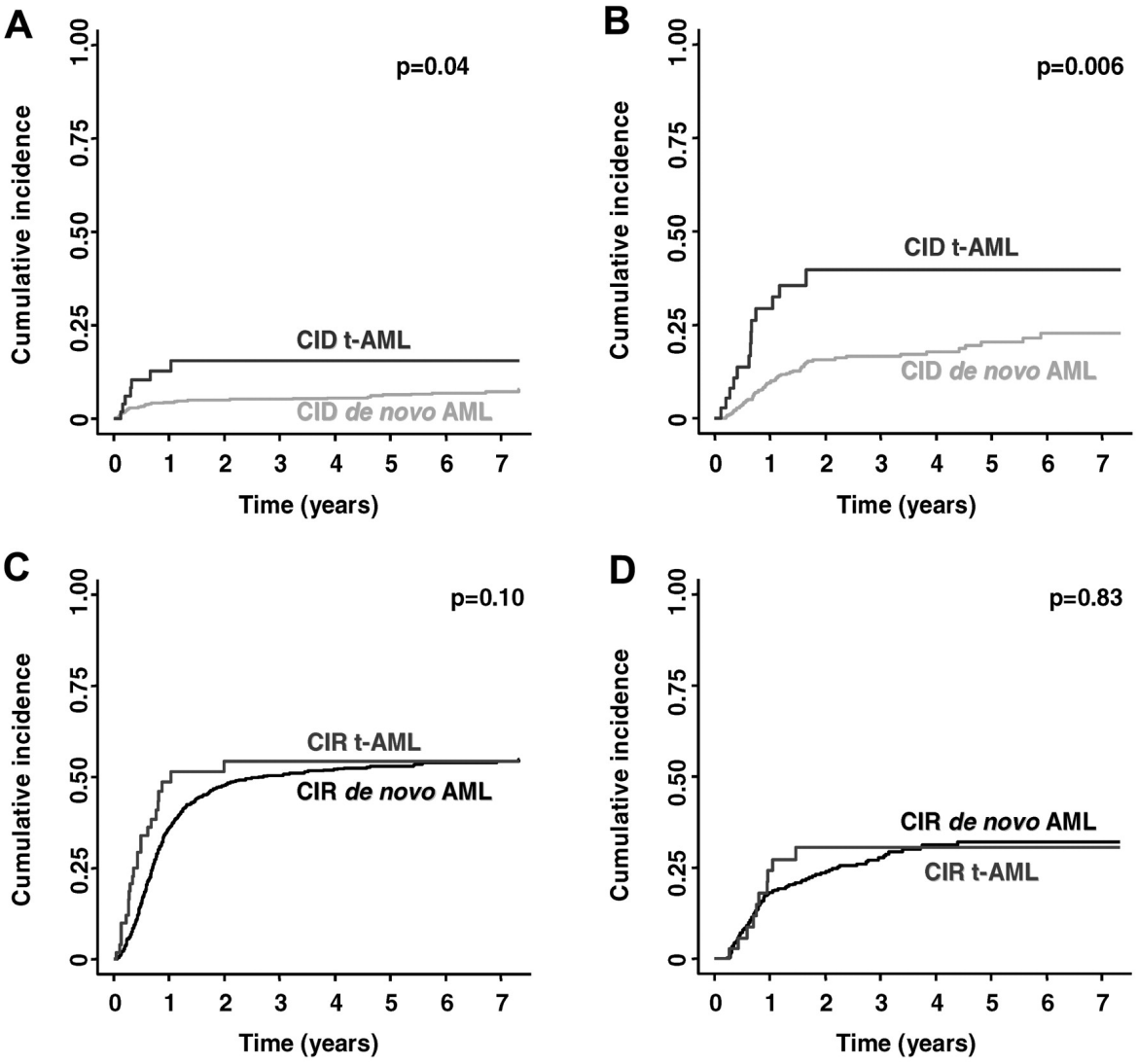
< 60 years

> 60 years

Sabine Kayser et al. Blood 2011;117:2137-2145

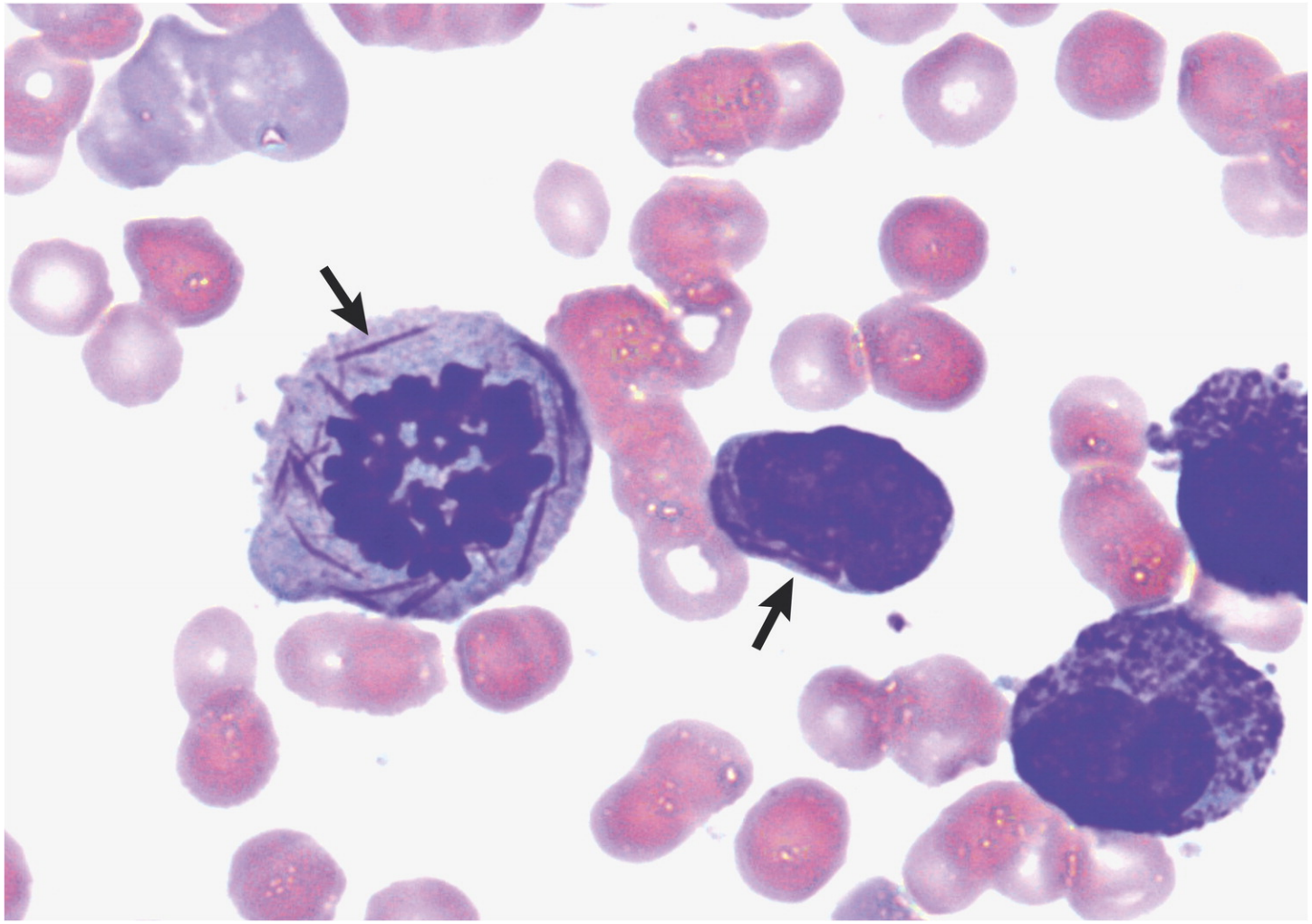
blood

Influence of AML type and postremission Rx on CID and CIR



Sabine Kayser et al. Blood 2011;117:2137-2145

Auer Rods



Gordon SW, Krystal GW. N Engl J Med 2017; 376:2065-2065.

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