Acute Promyelocytic Leukemia

BHS Course - Acute Leukemia - 16 December 2023

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Acute Leukemia and Transplant Team

Institut Jules Bordet - HUB

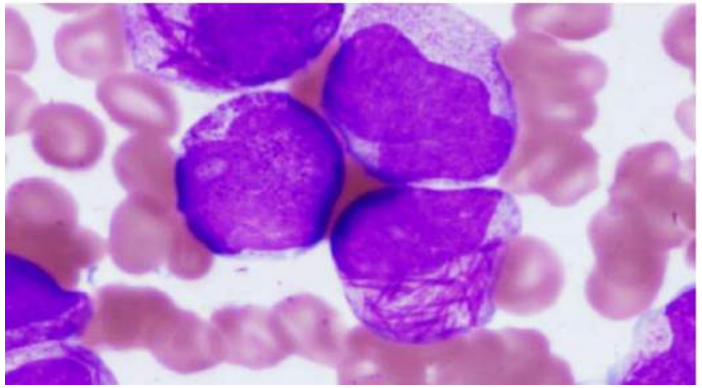
Emergency department

26 yo male patient
Spontaneous ecchymoses
Gincival bleeding
Petechiae
Weakness and effort dyspnoea

No other known disease

Hemoglobin	8.3 gr/dL
Platelets	54000/mcl
White blood cells	370/mcl
INR	1.5
aPTT	23 sec (NV 21.6 – 28.7 sec)
Fibrinogen	80 mg/dL
D-Dimer	15760 ng/mL

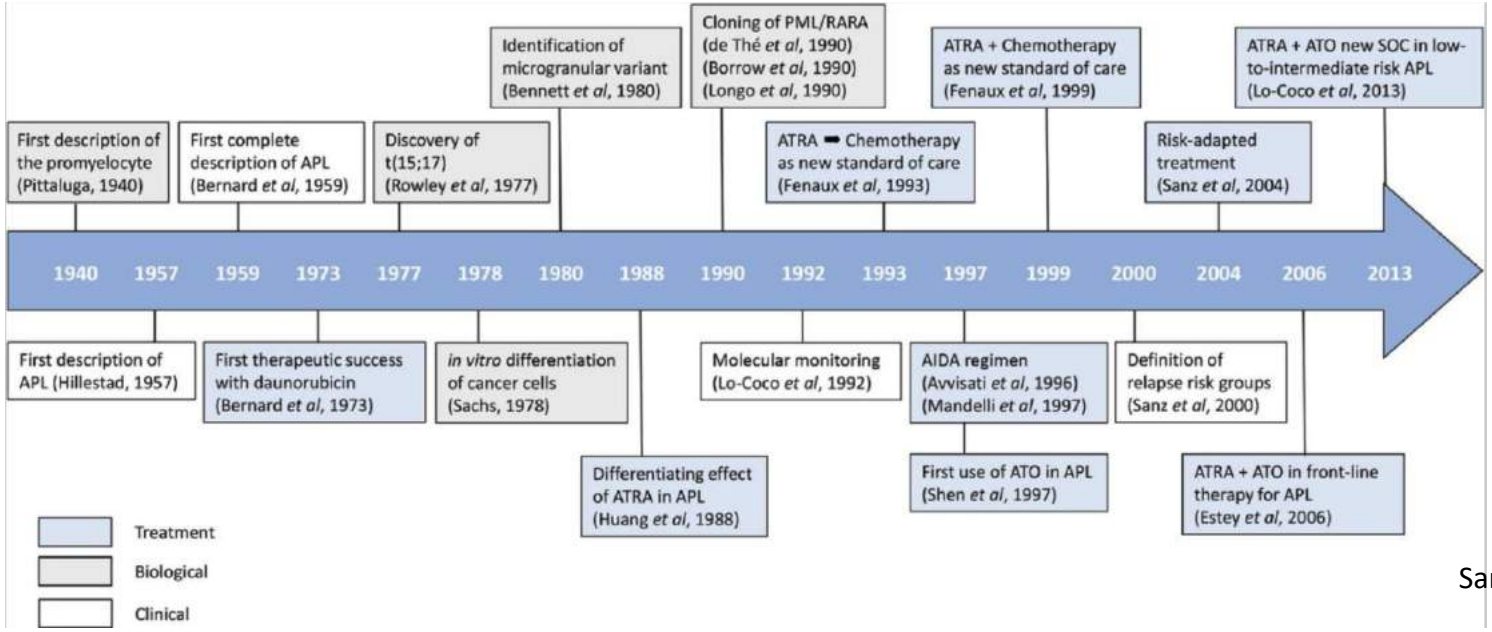
Bone Marrow: 80% myeloid blast infiltration



→ **Acute Promyelocytic Leukemia**

Acute Promyelocytic leukemia (APL)

- Distinct subtype of acute myeloid leukemia
- Medical Emergency
- Particular morphological features (two different morphologies)
- PML-RARα molecular hallmark
- APL is a model for oncogene-targeted leukemia cure



Sanz, Clin Hem Int 2021

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Acute Promyelocytic Leukemia.

By

LEIF K. HILLESTAD.

Acta Medica Scandinavica. Vol. CLIX, fasc. III, 1957.

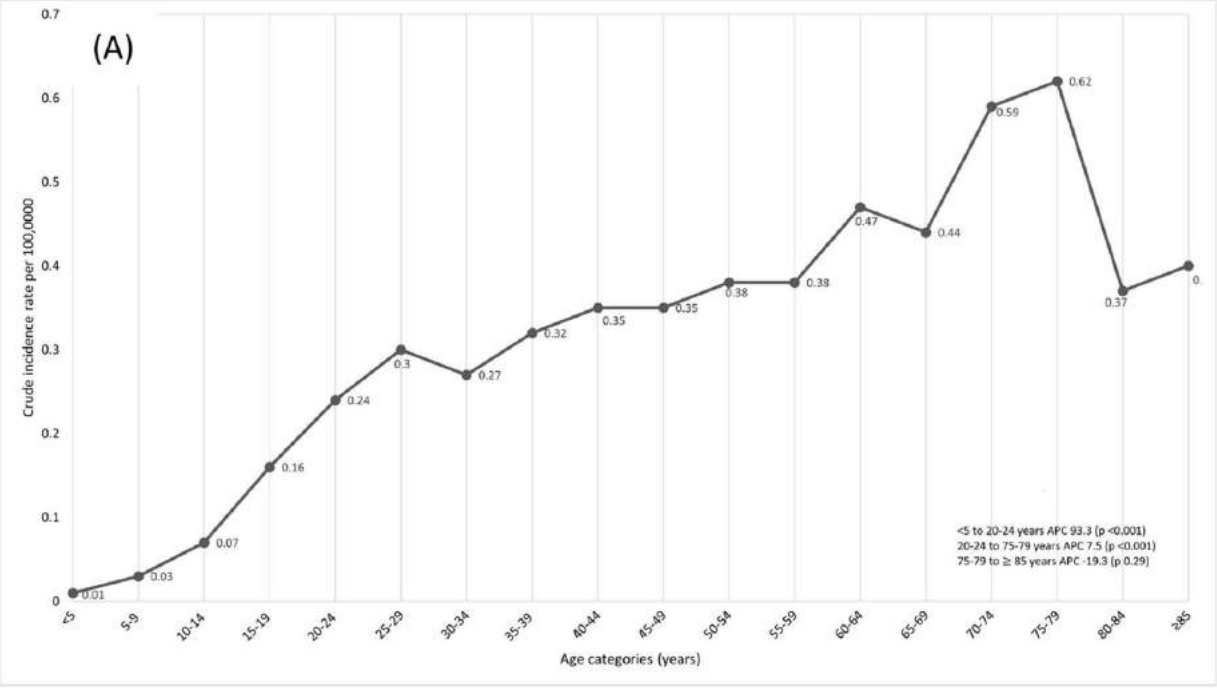
From the Medical Department A, Rikshospitalet, Oslo. Physician in chief: Professor P. A. Owren.

Evidence is presented for the existence of a special type of acute myelogenous leukemia. Three cases are described, characterized by 1) a very rapid fatal course of only a few weeks' duration, 2) a white blood cell picture dominated by promyelocytes, 3) a severe bleeding tendency due to fibrinolysis and thrombocytopenia.

It is suggested that this type is named acute promyelocytic leukemia. It seems to be the most malignant form of acute leukemia.

APL epidemiology

- 5 to 15 percent of cases of AML
- 0.32 new cases per 100,000 persons/ year in US
- Rare in childhood, increasing incidence from early adulthood
- May be secondary (15% in APL2006 trial)



Yamamoto JF, Goodman MT. Cancer Causes Control. 2008
Tedesco et al, Ther Adv Hematol 2011
Sharma et al Annals of Hematology 2023

Clinical Presentation

Symptoms related to **cytopenia** (weakness, neutropenic fever, bleeding)

Hemorrhagic findings (gingival bleeding, ecchymoses, epistaxis, or menorrhagia)

Thrombosis in about 5% of patients: most common are cerebral infarction, deep vein thrombosis, pulmonary embolism, and acute myocardial infarction.

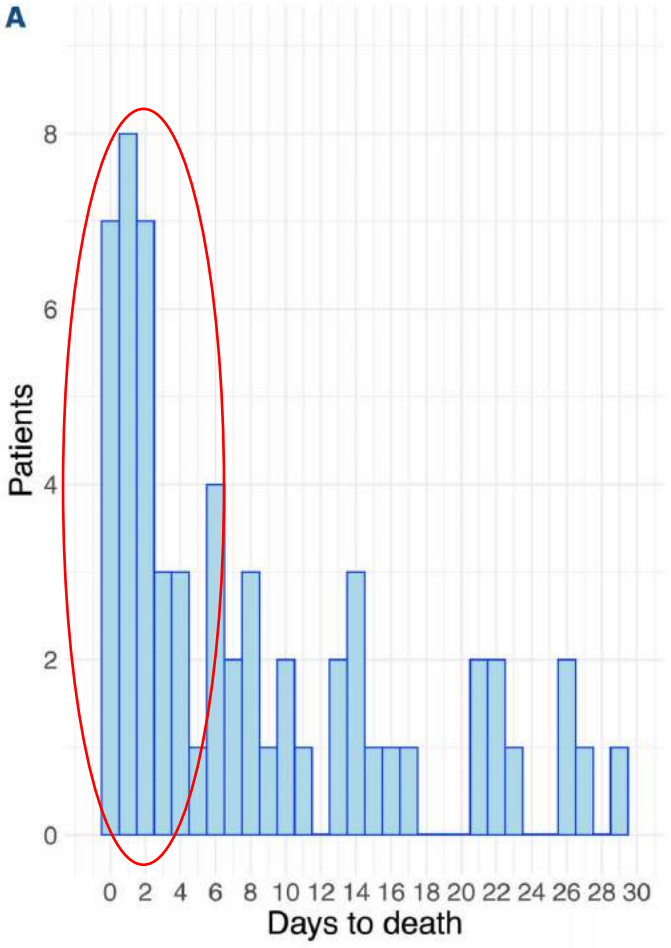
Biological Work-up

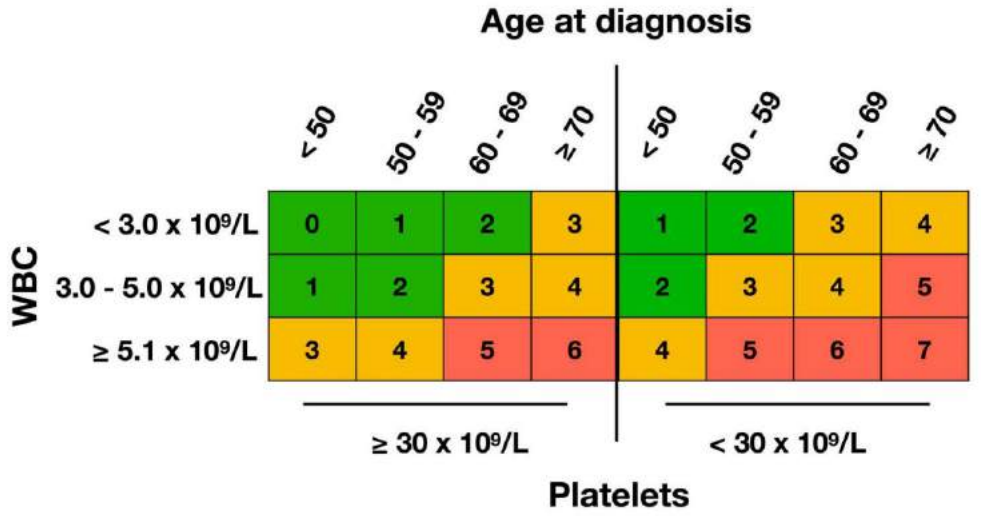
Pancytopenia, low number of circulating blasts despite massive bone marrow infiltration.

Coagulopathy (PT, PTT frequently prolonged, low fibrinogen and elevated D-dimers)

Breen et al BJH 2011
Hambley et al Frontiers 2021

Coagulopathy is responsable of early deaths in APL





Low risk	High risk	Very high risk
0 - 2 points	3 - 4 points	5 - 7 points
< 10 % predicted risk	10 - 30 % predicted risk	> 30 % predicted risk

Österroos et al. Haematologica 2022

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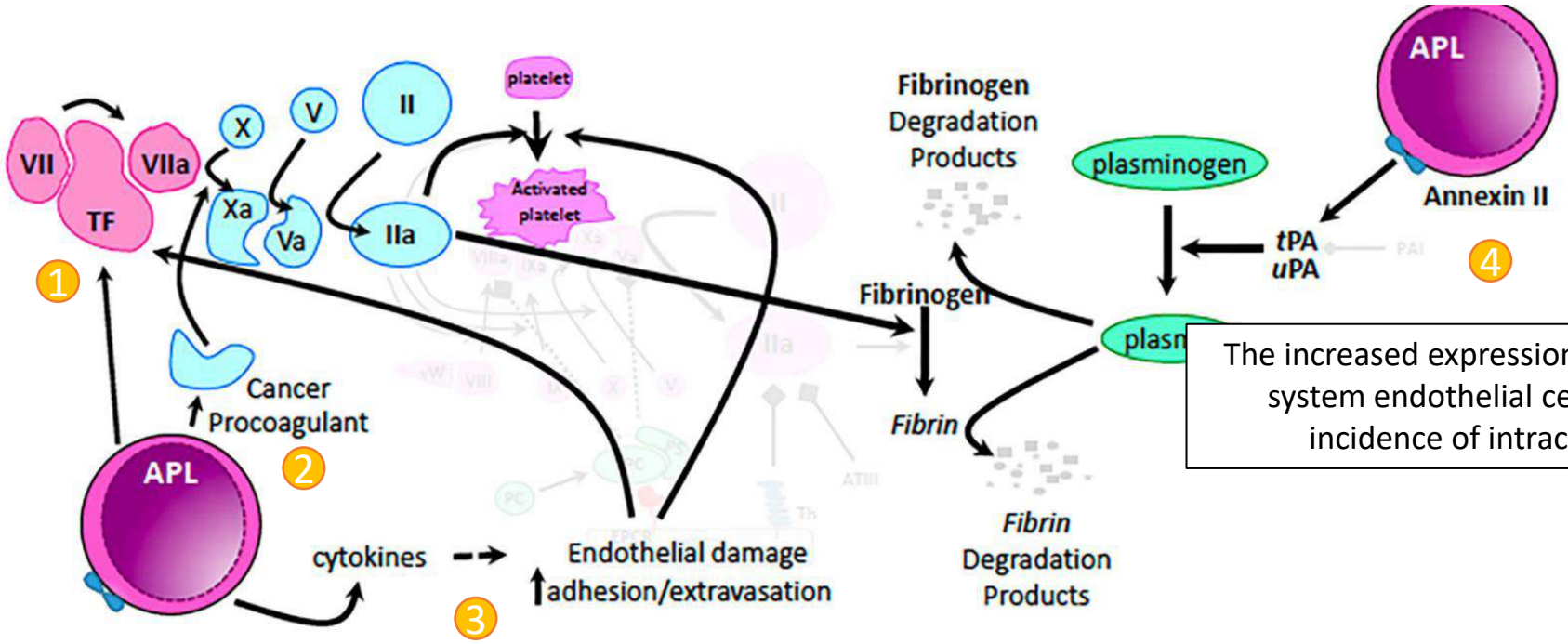
Activation of Coagulation

Increased fibrinolysis



The increased expression of annexin II on central nervous system endothelial cells may contribute to the high incidence of intracerebral hemorrhage in APL

1- TF - **100-fold more expressed in APL than in other blasts!**
2- Cancer pro coagulant
3- Cytokines
Massive amounts of IIa and consumptive coagulopathy.
4- Annexin II activates of tPA/uPA resulting in hyperfibrinolysis.

Hambley et al - Front. Med 2021

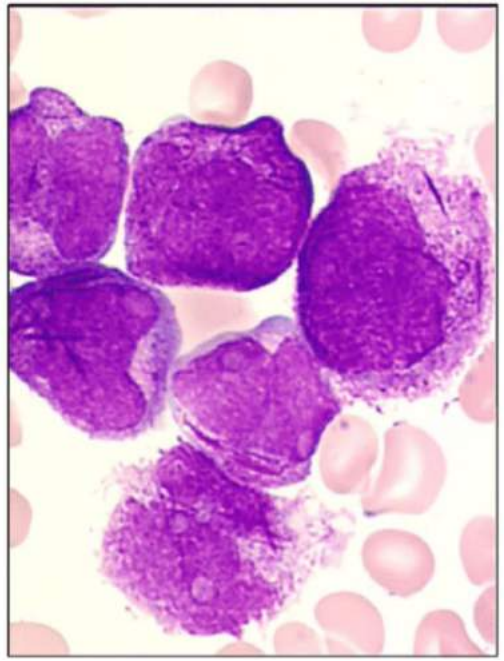
APL patients have significant lower WBC, higher D-dimers and lower Fibrinogen compared to other AML subtypes

Table 2. Comparison of the findings between APL patients and patients with other AML subtypes with DIC.

Variable	APL	Other AML subtype	*P*
Male/Female	5/9	9/6	0.272
Age (years)	49.3	57.5	0.23
WBC ($\times 10^9$/L)	14.988	70.755	0.015
Hb (g/dL)	8.03	7.36	0.412
Platelet ($\times 10^9$/L)	26.78	33.80	0.324
PT (s)	16.0	14.6	0.107
INR	1.43	1.26	0.071
aPTT (s)	28.7	29.6	0.691
FDP (μg/mL)	77.7	23.7	0.026
D-dimer (ng/mL)	7,376.2	1,315.2	0.018
Fibrinogen (mg/dL)	133.8	373.2	<0.001
LDH (U/L)	838.9	1,022.3	0.565
AST (U/L)	27.9	38.1	0.393
ALT (U/L)	21.0	36.3	0.305
Total bilirubin (mg/dL)	0.77	0.96	0.294
BUN (mg/dL)	16.6	21.1	0.518
Cr (mg/dL)	0.98	1.48	0.123
Triglyceride (mg/dL)	206.2	109.9	0.006
Cholesterol (mg/dL)	159	112	0.001
Fe (μg/dL)	135.4	120.0	0.469
TIBC (μg/dL)	264.4	206.8	0.046
Ferritin (ng/mL)	776.6	1,282.1	0.70
Transferrin (g/L)	1.79	1.29	0.005
CRP (mg/dL)	4.79	7.43	0.323
ESR (mm/h)	7.1	50.0	<0.001

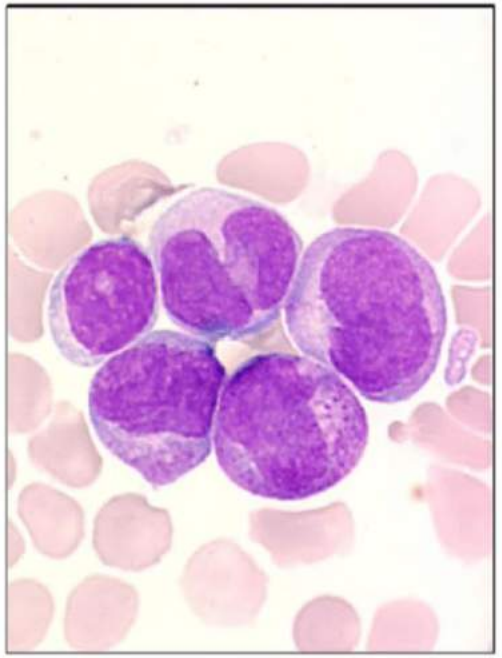
Lee Blood Res 2013

75% typical (macrogranular) – M3



Low white blood cell count
Reniform nuclei
Purple granulations and Auer roads, faggots

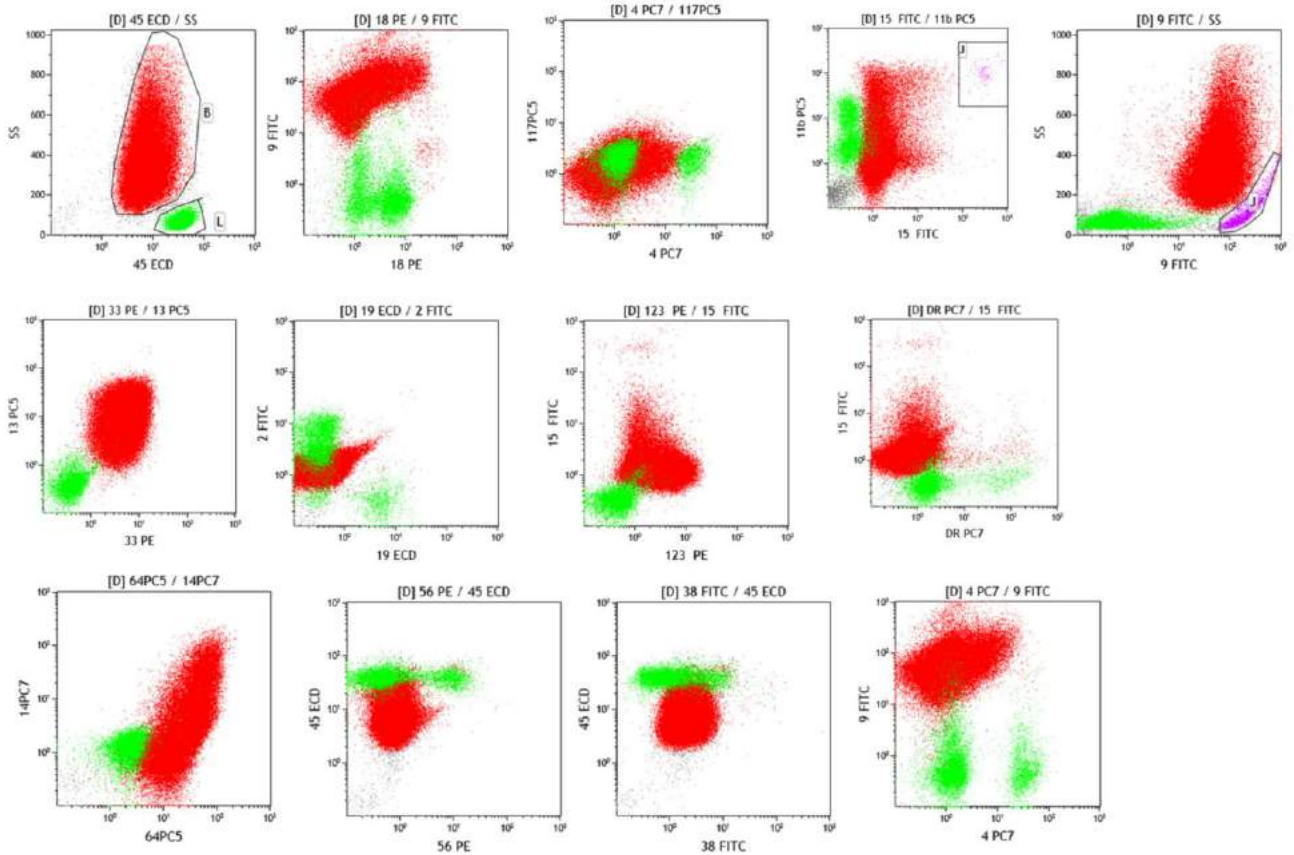
25% microgranular variant – M3v



Higher white blood cell count
Reniform nuclei
Few granulations (better seen at electronic microscope)

Sainty et al Blood. 2000
Xavier Onc and Ther 2019

CD34-/partial or weak +, HLA-DR -, CD13+, CD33+, CD11b-, CD15-, CD117 weak/variable, MPO+.



<u>100% sensitivity and 99% specificity for APL</u>

CD33 targable with Gemtuzumab Ozogamicin

Lin et al Am J Clin Pathol. 2004
Sainty et al Blood. 2000
Ferrara et al J Clin Oncol. 2000
https://www.flowcytometrynet.com/apl

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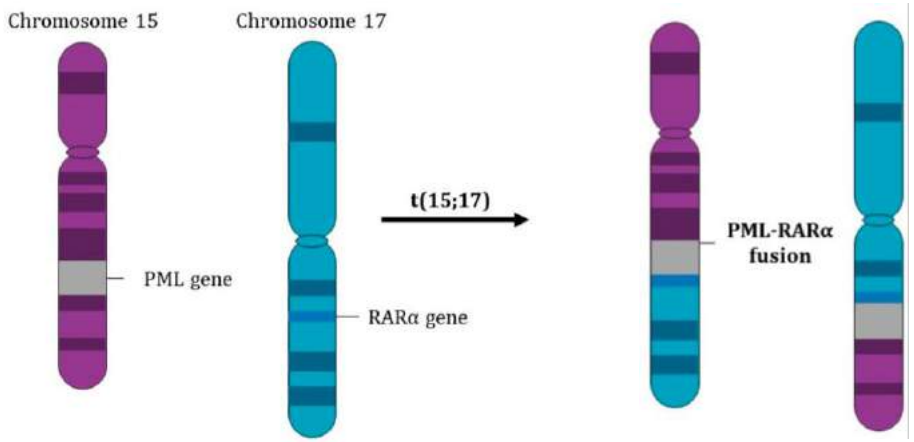
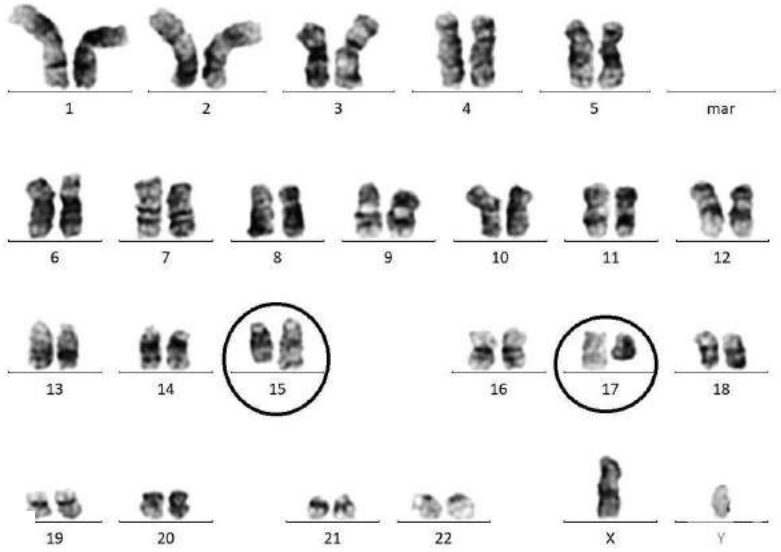
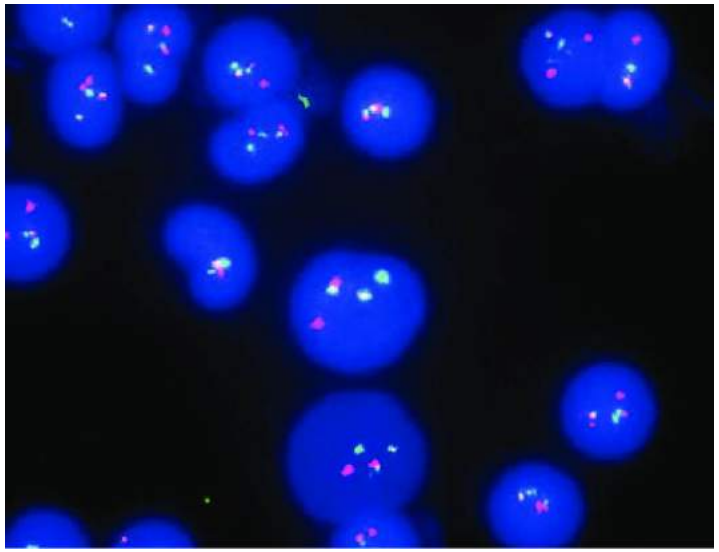
Translocation t(15;17)(q24;q21)







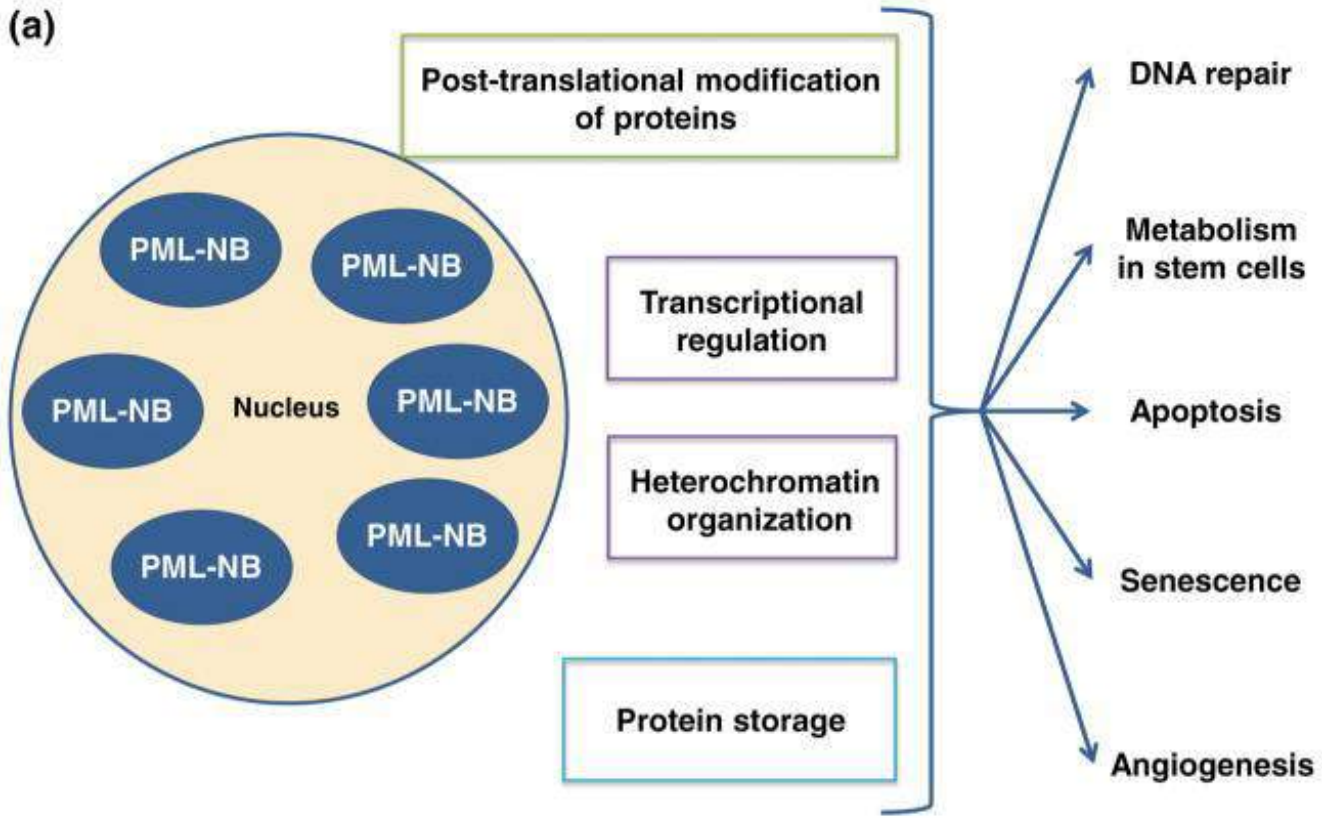
PML
RARα
PML/RARα

https://imagebank.hematology.org/

Dauare et al Future Pharmacol. 2023

Ye sun Medecine 2021

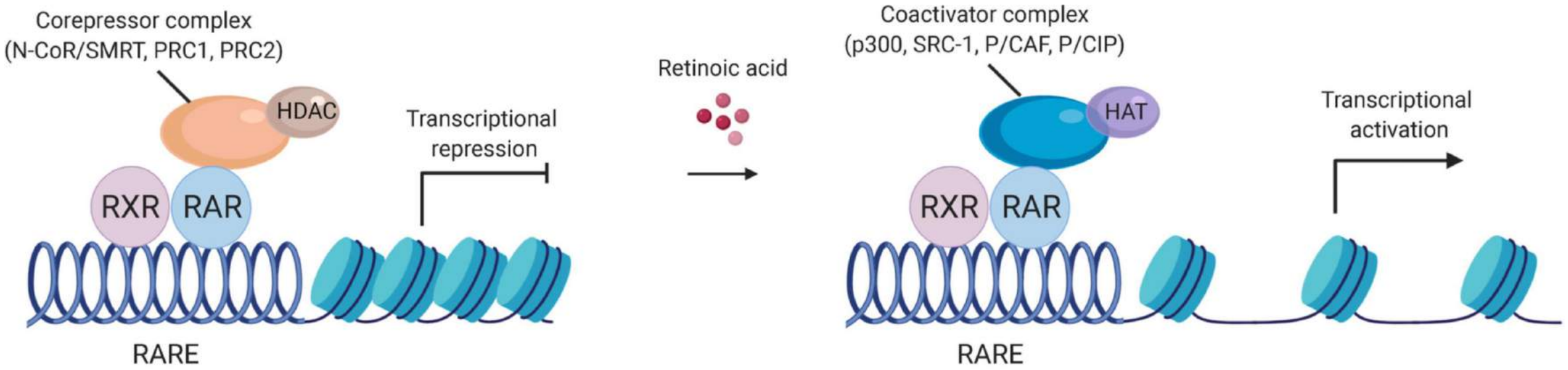
PML proteins multimerize to form multi-protein sub-nuclear structures called PML-nuclear bodies



Lallemand-Breitenbach Persp Biol. 2010

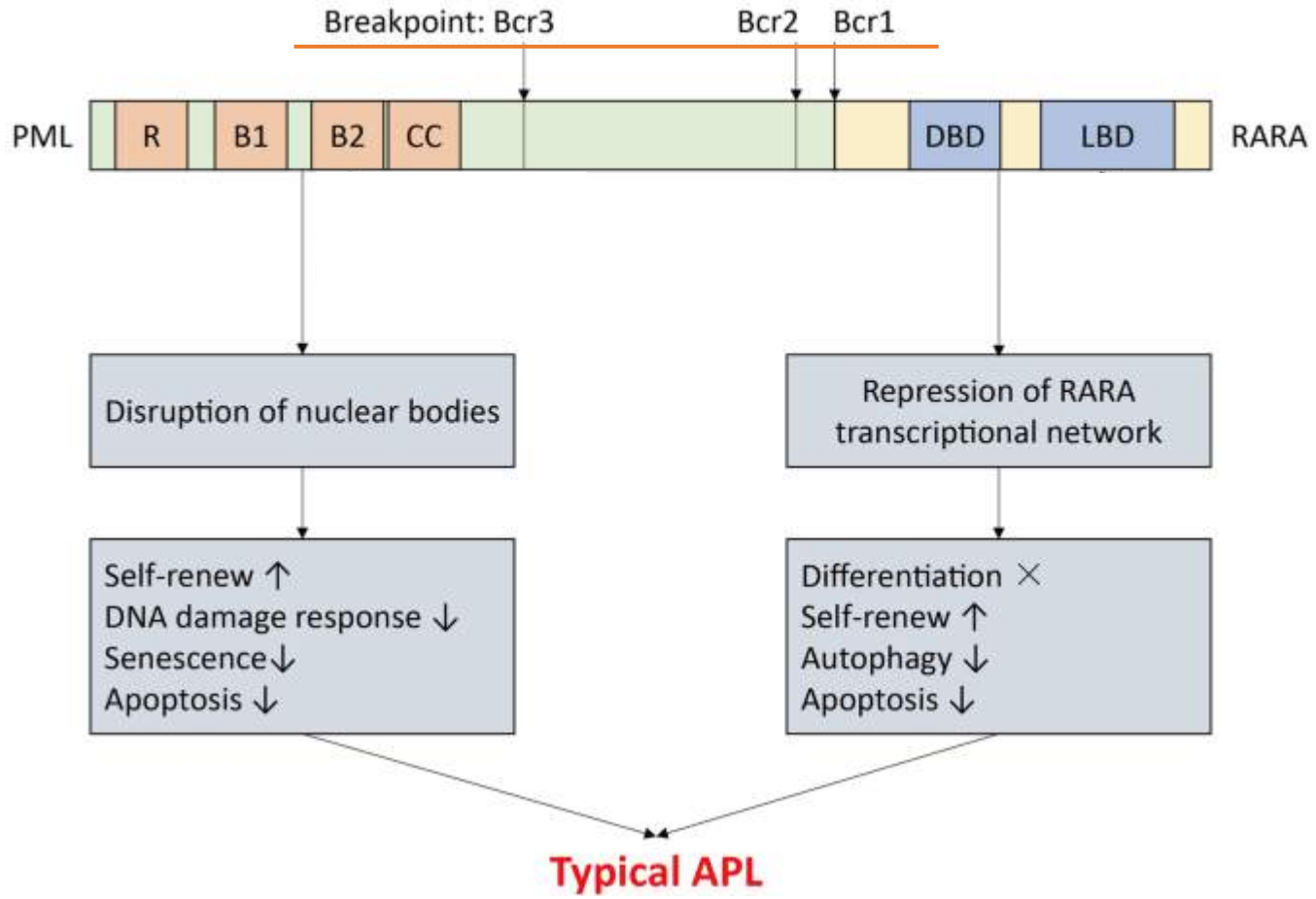
Bernardi R et al Nat Rev Mol Cell Biol. 2007 Nakahara Int Jour of Hem 2014

RARα promotes transcriptional activation and myeloid differentiation in physiological conditions



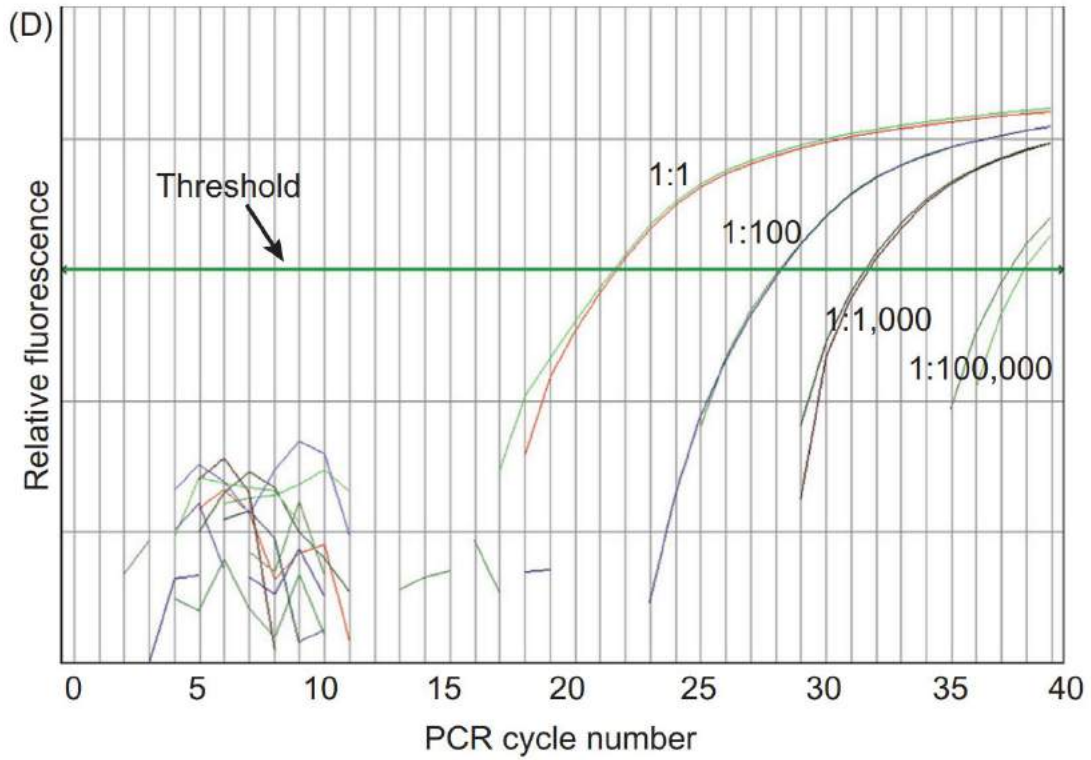
Myeloid differentiation

PML-RARA/t(15;17)



Zhang et al Biomarker Research 2021

PML/RARα as marker of Minimal Residual Disease (MRD)

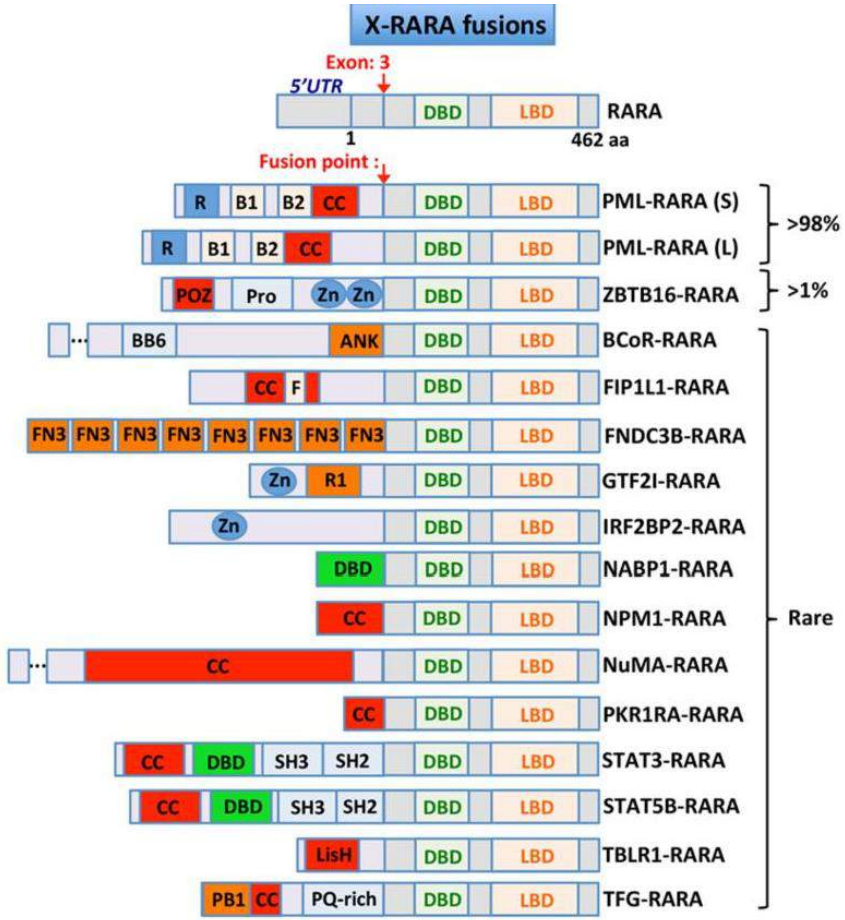


Behdad and Betz, Diagnostic Molecular Pathology 2017

PML-RARα

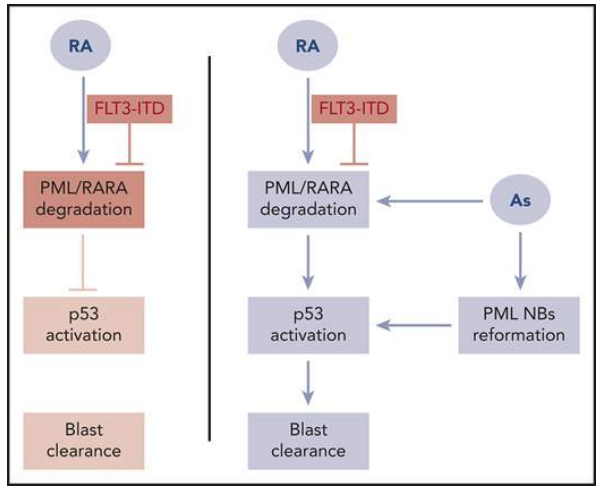
- Unique to APL (disease hallmark)
- Strongly correlated with pathogenesis
- Ideal marker for residual disease monitoring
- Targeted by specific therapies

APL variants



Geoffroy et al Cancers 2020

Associated mutations



FLT3 – ITD

Confers R to ATRA-induced differentiation, abrogated with ATO

More likely to present with high white blood count

WT1 mutation

In association with FLT3mut, worsens prognosis

Esnault et al Blood 2019 Gale Blood 2005 Yoon Clin Res Inf Serv 2017 Picharski et al Cancers 2019

APL Treatment Evolution, moving towards a chemo-free strategy

- Anthracyclines
- ATRA
- ATRA + Chemotherapy (IDA)
- ATO
- ATRA+ ATO in non-high risk patients
- ATRA+ ATO+/- chemo (GO/IDA) and ATRA-ATO in all risk APL

Anthracyclines as APL treatment

BLOOD *The Journal of Hematology*

VOL. XLI, NO. 4 APRIL 1973

Acute Promyelocytic Leukemia: Results of Treatment by Daunorubicin

By Jean Bernard, Marise Weil, Michel Boiron, Claude Jacquillat, Georges Flandrin, and Marie-François Gemon

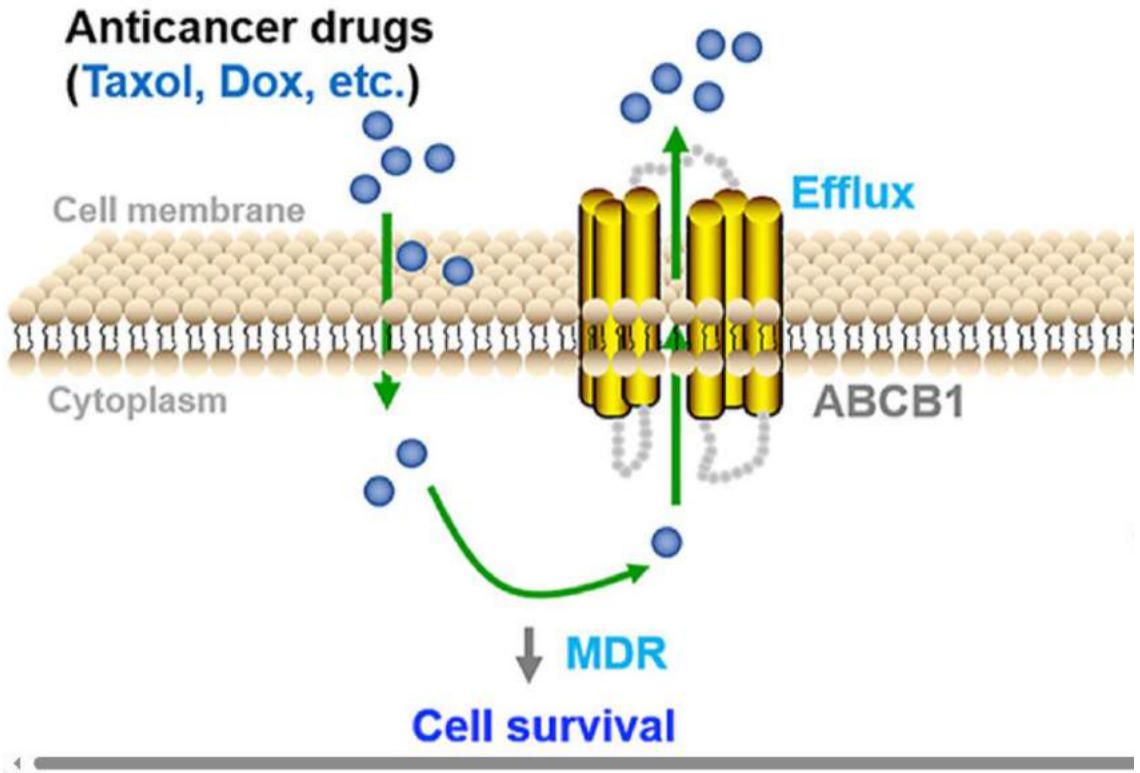
Jean Bernard: Daunorubicin + massive platelet transfusions

- Up to 80% CR, 40 to 50% prolonged CR
- High sensitivity of APL to anthracyclines

British Journal of Haematology, 1995, 90, 369–374

Low incidence of MDR1 expression in acute promyelocytic leukaemia

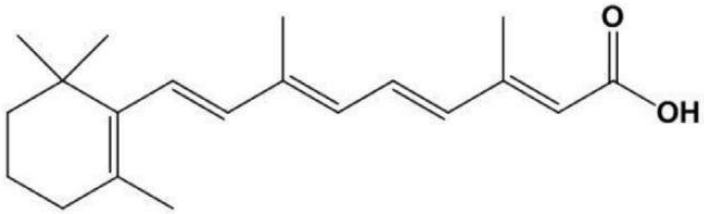
Doris Drach, Shourong Zhao, Johannes Drach and Michael Andreeff *Department of Hematology, Section of Experimental Hematology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, U.S.A.*



Wu et al, Acta Pharmaceutica Sinica B 2021

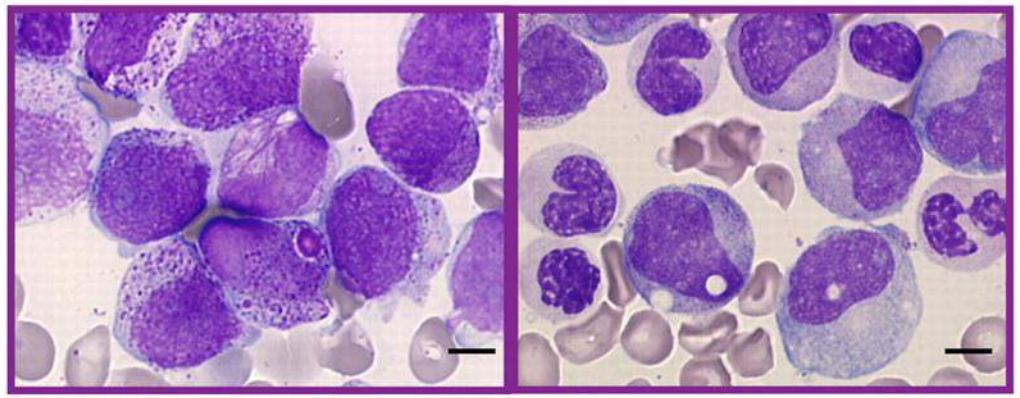
All-trans retinoic acid (ATRA)

- Vitamin A derivative, differentiation induction



ATRA

- 1988: All transretinoic acid (ATRA)
  - 90% complete remissions, through differentiation of APL cells
  - No long-lasting CR, relapsed within a few months, despite continuous ATRA treatment



Huang, Blood, 1988

Continuous Treatment With All-*Trans* Retinoic Acid Causes a Progressive Reduction in Plasma Drug Concentrations: Implications for Relapse and Retinoid "Resistance" in Patients With Acute Promyelocytic Leukemia

By Josephia Muindi, Stanley R. Frankel, Wilson H. Miller Jr, Ann Jakubowski, David A. Scheinberg, Charles W. Young, Ethan Dmitrovsky, and Raymond P. Warrell Jr

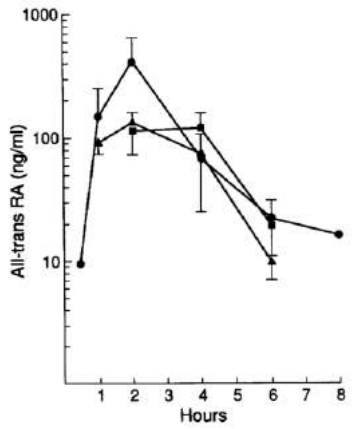


Fig 1. Plasma concentrations (±SEM) of all-*trans* RA after the administration of a single oral dose (45 mg/m²) on day 1 of treatment in three patients (●), at the time of relapse (▲), and at relapse (■) after treatment with a single dose of 90 mg/m². The calculated plasma AUC concentrations were significantly lower at the time of relapse compared with day 1 and were not increased despite the twofold escalation in dose.

Decrease in ATRA plasma levels in prolonged administration.

ATRA induced increase of CytP450 which catabolises ATRA.

→ATRA-Chemotherapy combination

→ATRA **intermittently** administered rather than continuously in maintenance therapy.

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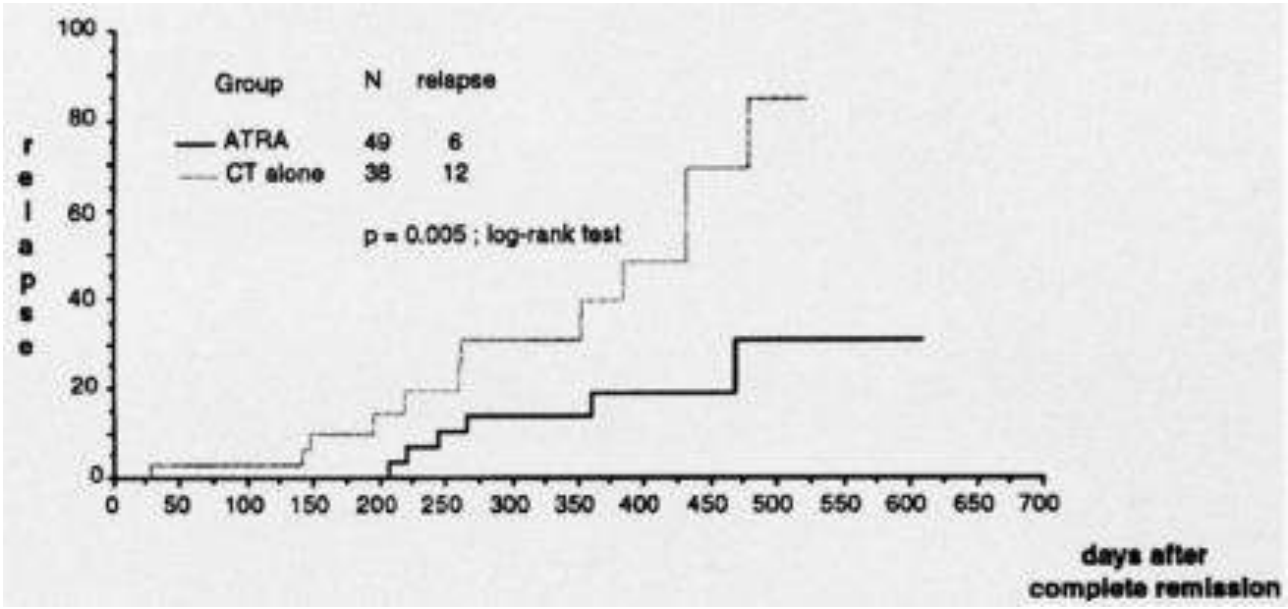
ATRA + Chemotherapy

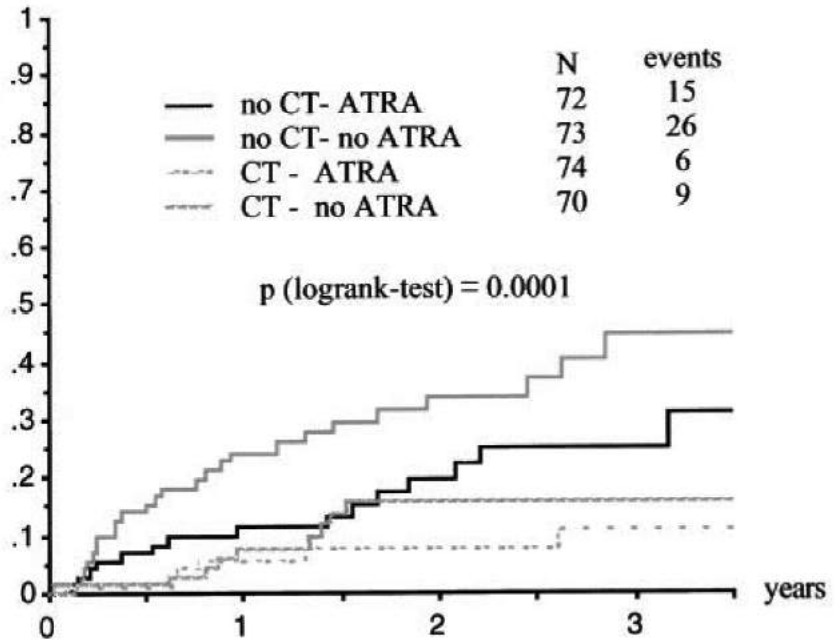
- 1991: ATRA+ chemotherapy better than chemotherapy alone
- 90% CR, 25 % relapses



Fenaux, Blood 1993

Maintenance with ATRA

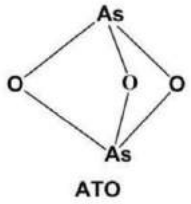
- 1997: maintenance treatment with ATRA and low dose chemotherapy reduces relapses



Relapse according to maintenance treatment group

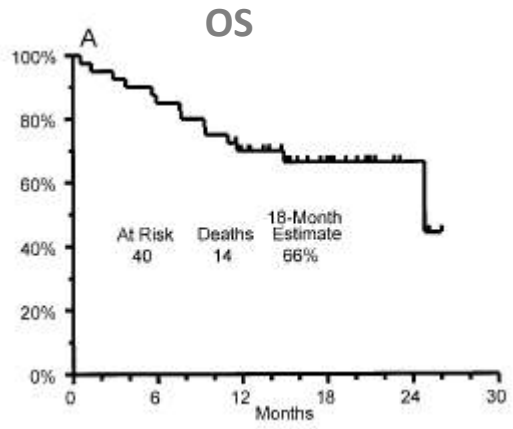
Fenaux et al, Blood, 1999

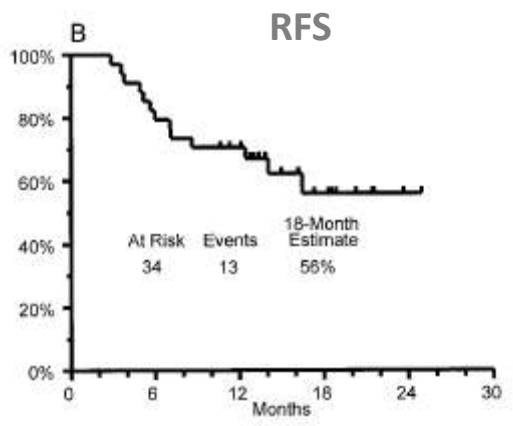
Arsenic trioxide (ATO) in APL



ATO

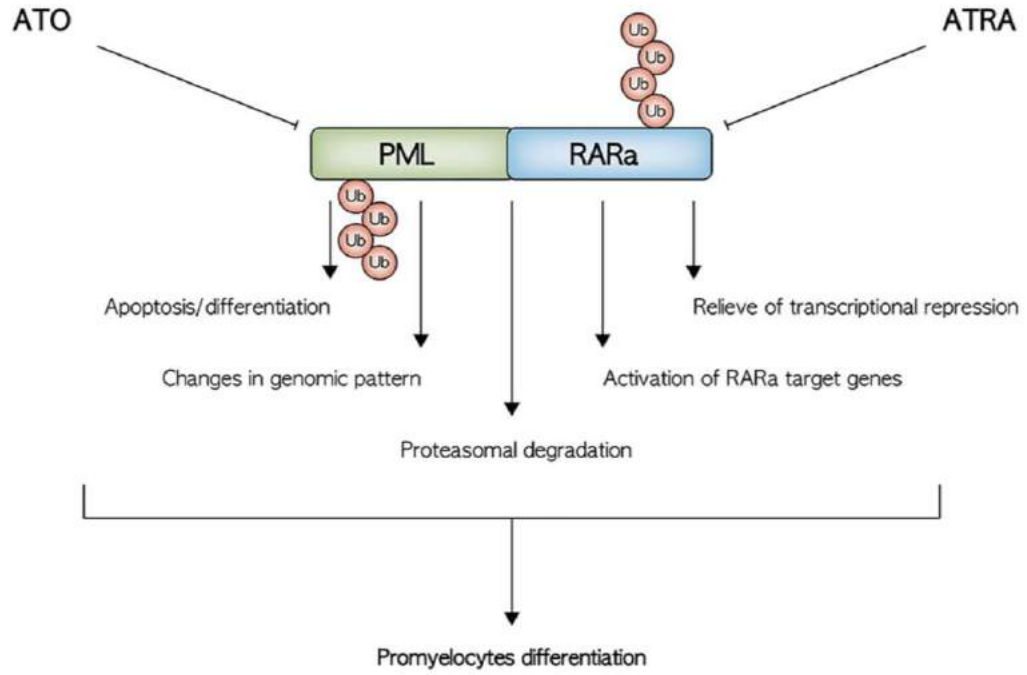
- High efficacy of ATO in APL reported in 1992 by a Chinese study, confirmed in a randomized US study
- Approved by FDA for relapsed APL in 2000





Soignet et al., JCO 2001

- ATRA and ATO both degrade PML/RARA
  - ATRA degrades PML/RARA through its RARA moiety and relieve transcriptional repression
  - ATO degrades PML/RARA through its PML moiety



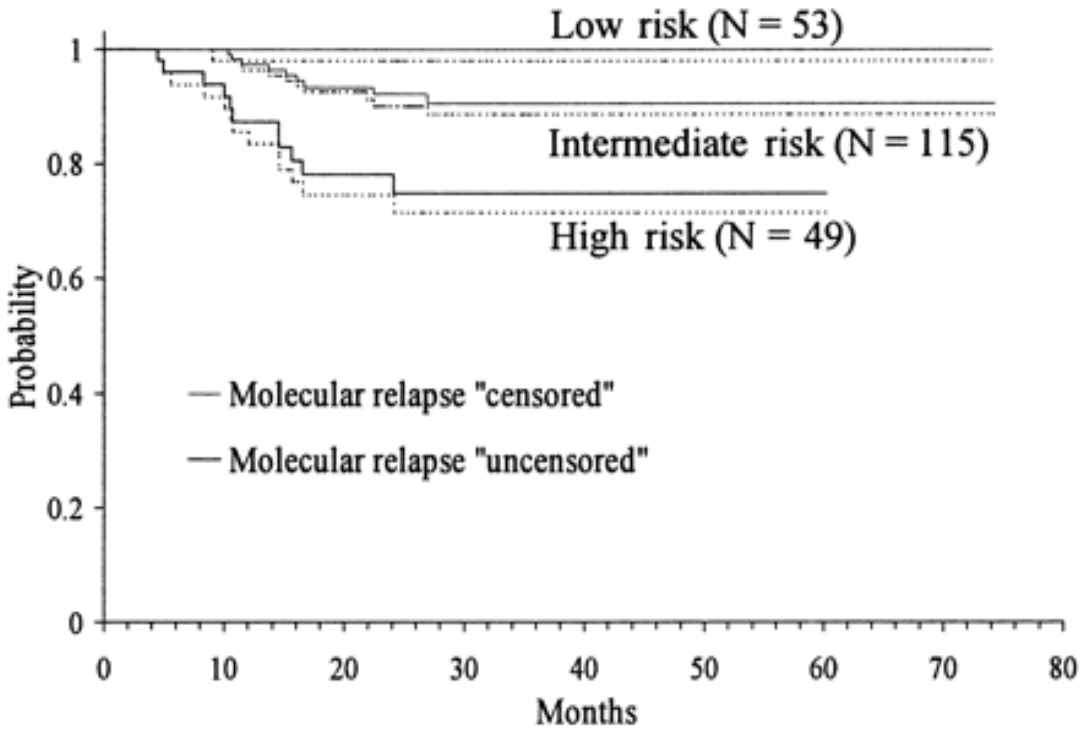
Masetti et al Front. Oncol. 2023

Risk-assessment, "Sanz-score"

- **High risk:**
  WBC >10.000/mm3

- **Int risk:**
  WBC< 10.000/mm3
  Platelets <40.000/mm3

- **Low risk:**
  WBC< 10.000/mm3 and
  Platelets >40.000/mm3



Sanz et Lo Coco, Blood 2000

APL0406 randomized trial for NON-high risk patients

The NEW ENGLAND JOURNAL of MEDICINE

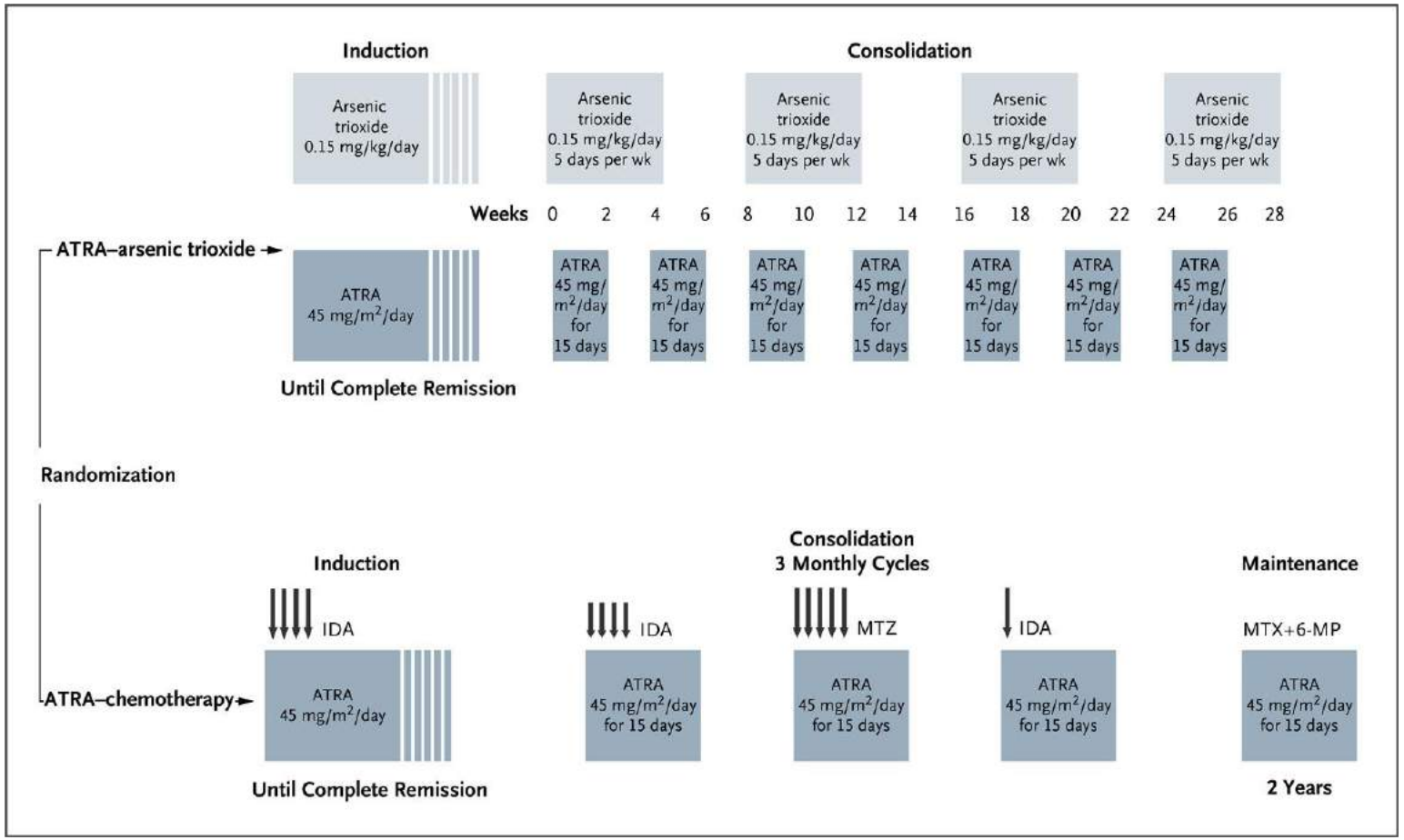
ESTABLISHED IN 1812 JULY 11, 2013 VOL. 369 NO. 2

Retinoic Acid and Arsenic Trioxide for Acute Promyelocytic Leukemia

F. Lo-Coco, G. Avvisati, M. Vignetti, C. Thiede, S.M. Orlando, S. Iacobelli, F. Ferrara, P. Fazi, L. Cicconi, E. Di Bona, G. Specchia, S. Sica, M. Divona, A. Levis, W. Fiedler, E. Cerqui, M. Breccia, G. Fioritoni, H.R. Salih, M. Cazzola, L. Melillo, A.M. Carella, C.H. Brandts, E. Morra, M. von Lilienfeld-Toal, B. Hertenstein, M. Wattad, M. Lübbert, M. Hänel, N. Schmitz, H. Link, M.G. Kropp, A. Rambaldi, G. La Nasa, M. Luppi, F. Ciceri, O. Finizio, A. Venditti, F. Fabbiano, K. Döhner, M. Sauer, A. Ganser, S. Amadori, F. Mandelli, H. Döhner, G. Ehninger, R.F. Schlenk, and U. Platzbecker for Gruppo Italiano Malattie Ematologiche dell'Adulto, the German–Austrian Acute Myeloid Leukemia Study Group, and Study Alliance Leukemia

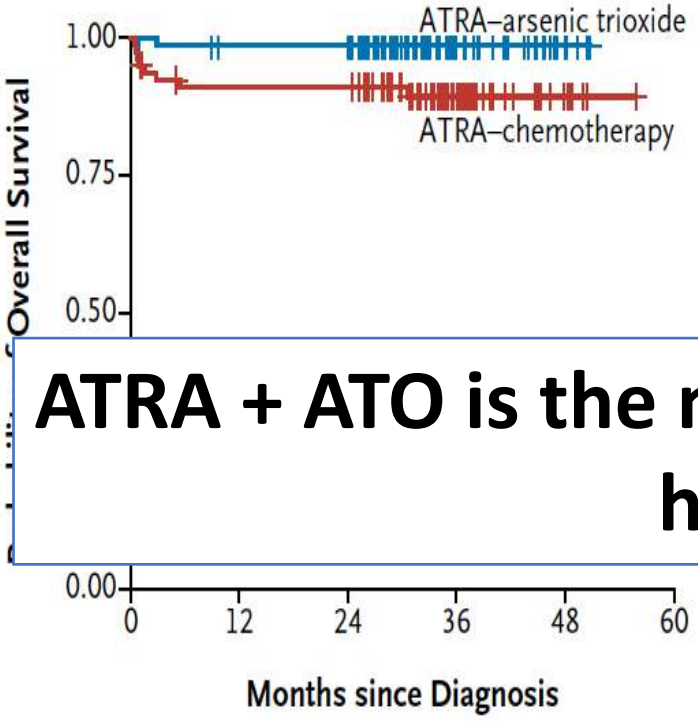
APL0406 randomized trial for NON-high risk patients ATRA-ATO versus AIDA

APL
Low/intermediate Sanz risk
(WBC ≤10 x 10^9/L)

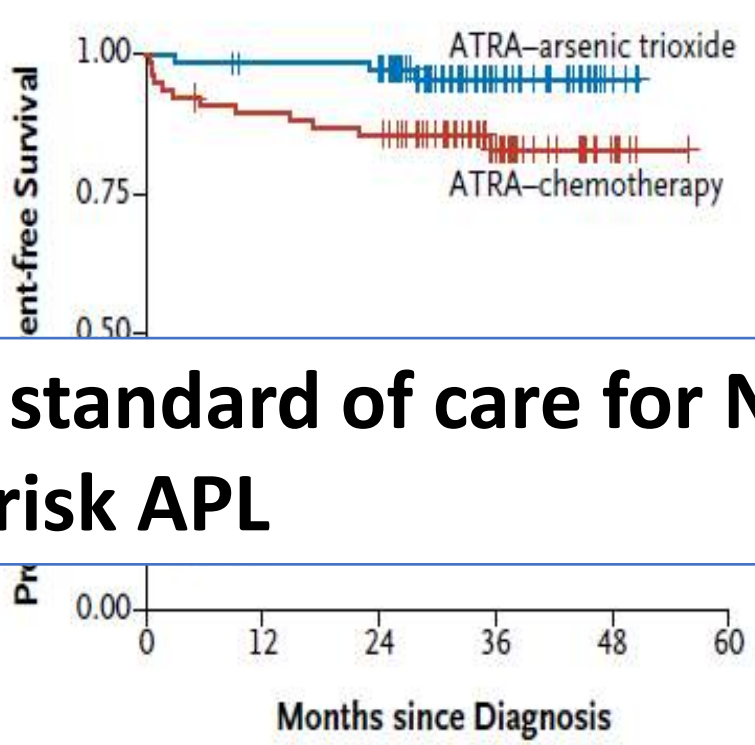


Lo Coco , NEJM 2013

OS



EFS



NON-high risk patients

ATRA + ATO is the new standard of care for NON high risk APL

ATRA + ATO is at least not inferior and may be superior to ATRA + CHT in the treatment of patients with low-to-intermediate-risk APL

Advantage in terms of EFS, relapse rate and OS at 50 mo in final analysis (276 pts)

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Lo Coco , NEJM 2013
Platzbecker, JCO 2017

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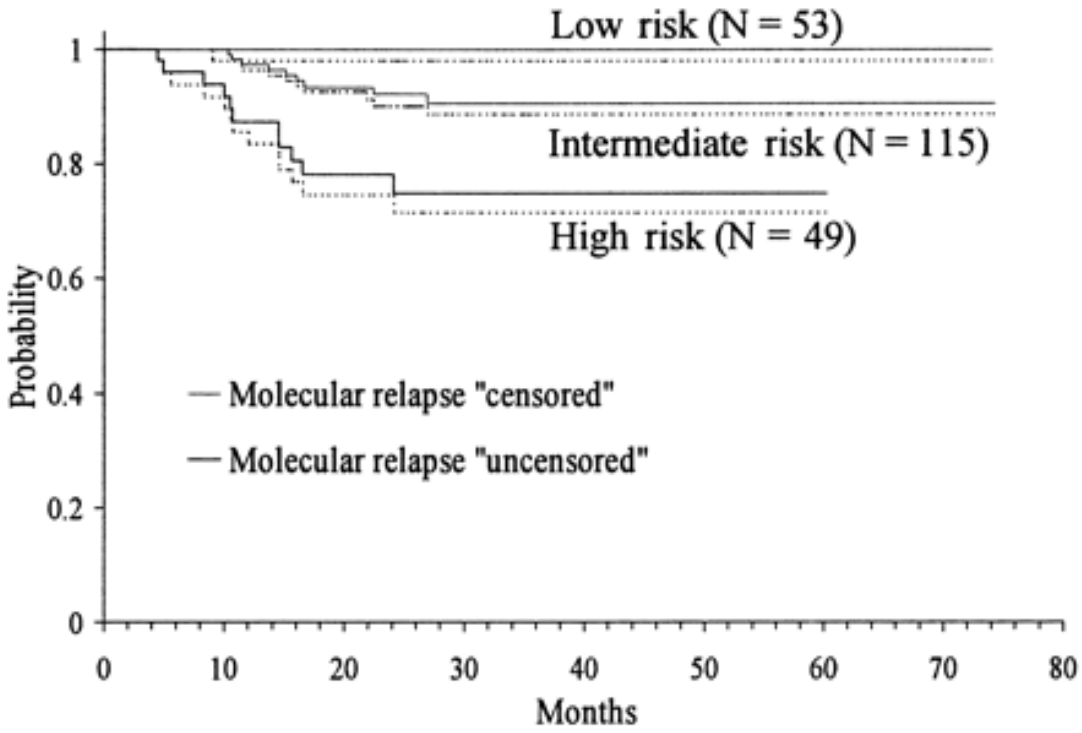
Risk-assessment, "Sanz-score"

- **High risk:**
  WBC >10.000/mm3
- Int risk:

Concerns about higher possibility of induction mortality due to increased risk of fluid overload, differentiation syndrome, respiratory failure, disseminated intravascular coagulation (DIC), and severe bleeding.



Sanz et Lo Coco, Blood 2000

All-*trans*-retinoic acid, idarubicin, and IV arsenic trioxide as initial therapy in acute promyelocytic leukemia (APML4)

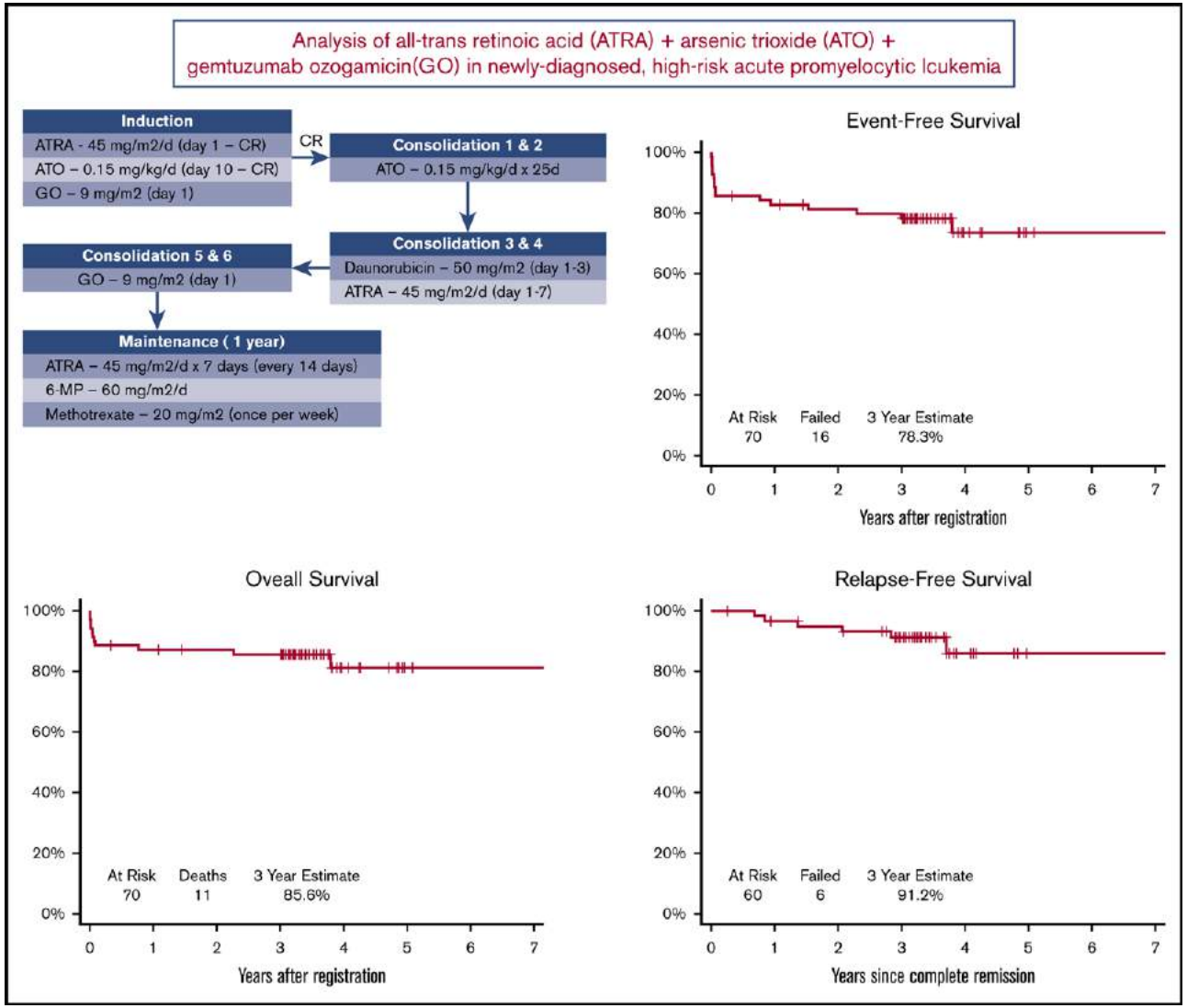
Harry J. Iland,[1,2] Ken Bradstock,[2,3] Shane G. Supple,[1] Alberto Catalano,[1] Marnie Collins,[4] Mark Hertzberg,[2,3] Peter Browett,[5] Andrew Grigg,[6,7] Frank Firkin,[7,8] Amanda Hugman,[1] John Reynolds,[4] Juliana Di Iulio,[4] Campbell Tiley,[9,10] Kerry Taylor,[11] Robin Filshie,[7,8] Michael Seldon,[10,12] John Taper,[13] Jeff Szer,[6,7] John Moore,[14,15] John Bashford,[16] and John F. Seymour,[4,7] for the Australasian Leukaemia and Lymphoma Group

Table 1. Components of the APML4 protocol

Induction		
ATRA	45 mg/m²/d PO	Days 1-36 in divided doses
Idarubicin	12 mg/m²/d IV (ages 1-60) 9 mg/m²/d IV (ages 61-70) 6 mg/m²/d IV (ages > 70)	Days 2, 4, 6, and 8
ATO	0.15 mg/kg/d IV	Days 9-36 as a 2-hour IV infusion Supplemental potassium and magnesium as required to maintain serum levels in the upper half of the respective normal ranges
Prednisone	1 mg/kg/d PO	Days 1-10 or until WBC count falls below 1 × 10^9/L or until resolution of differentiation syndrome (whichever occurs last)
Hemostatic support	Products administered once or twice daily as required to achieve specified targets	Platelets > 30 × 10^9/L Normal prothrombin time Normal activated partial thromboplastin time Fibrinogen > 1.5 g/L
Consolidation cycle 1 (3-4 wks after the end of induction)		
ATRA	45 mg/m²/d PO	Days 1-28
ATO	0.15 mg/kg/d IV	Days 1-28
Consolidation cycle 2 (3-4 wks after the end of consolidation cycle 1)		
ATRA	45 mg/m²/d PO	Days 1-7, 15-21, 29-35
ATO	0.15 mg/kg/d IV	Days 1-5, 8-12, 15-19, 22-26, 29-33
Maintenance: 8 cycles (3-4 wks after the end of consolidation cycle 2)		
ATRA	45 mg/m²/d PO	Days 1-14
MTX	5-15 mg/m²/wk PO	Days 15-90
6MP	50-90 mg/m²/d PO	Days 15-90

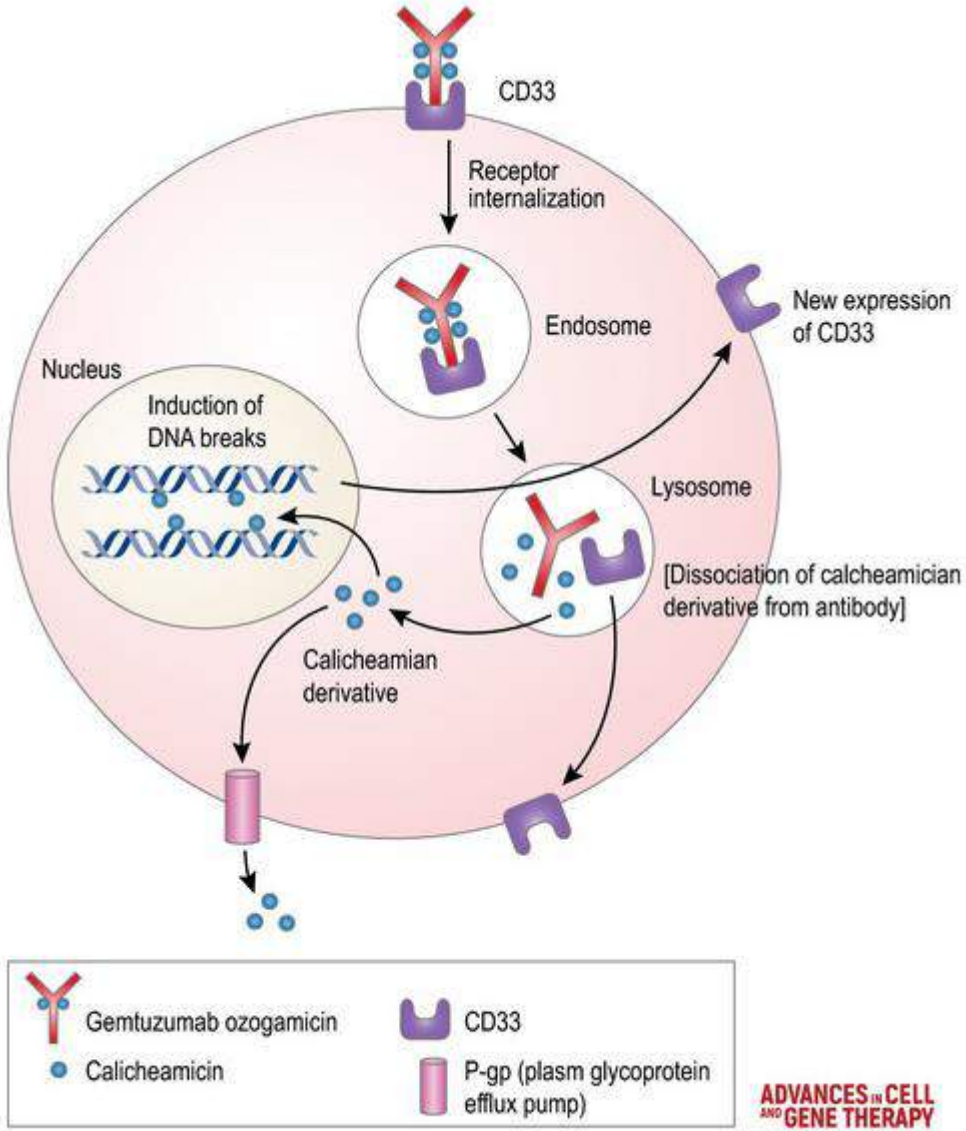
PO indicates oral administration.

Excellent outcomes despite a substantial reduction in anthracycline exposure.



Lancet et al Blood Adv, 2020

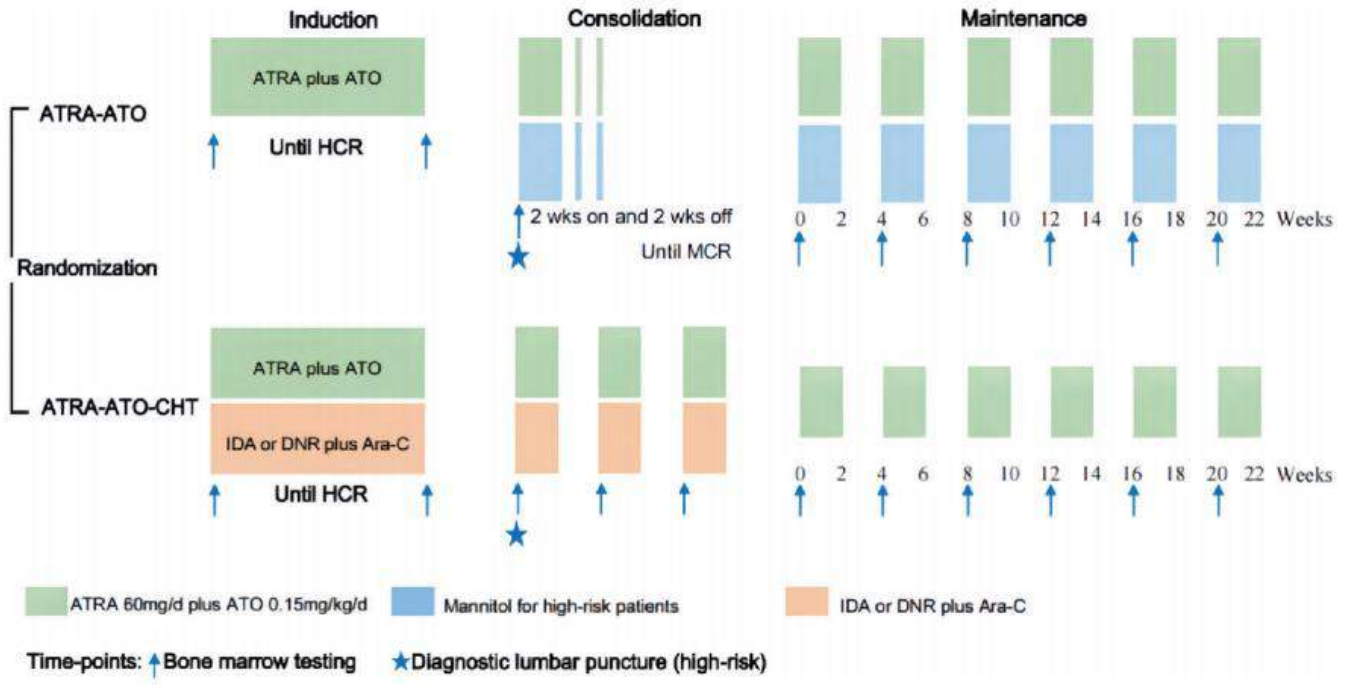
Gemtuzumab Ozogamicin

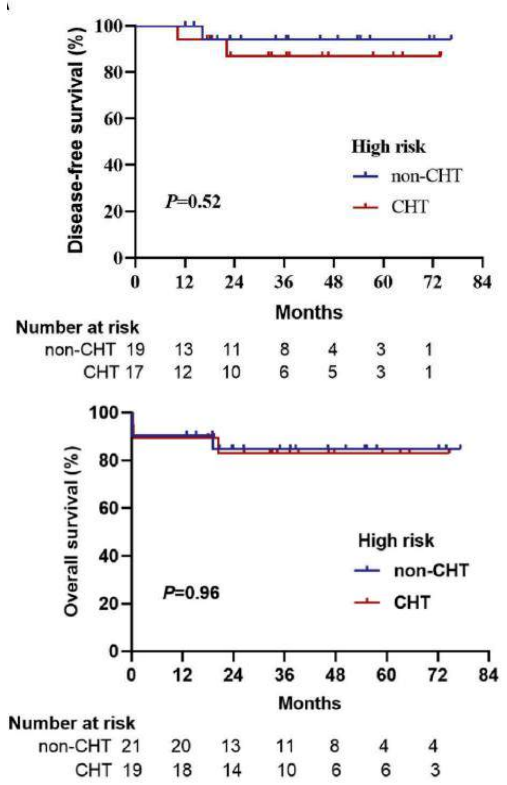


ADVANCES IN CELL AND GENE THERAPY

Boddu et Ravandi Adv Cell Gene Ther 2018

APL15 – ALL risk APL patients, ATRA-ATO +/- CHT

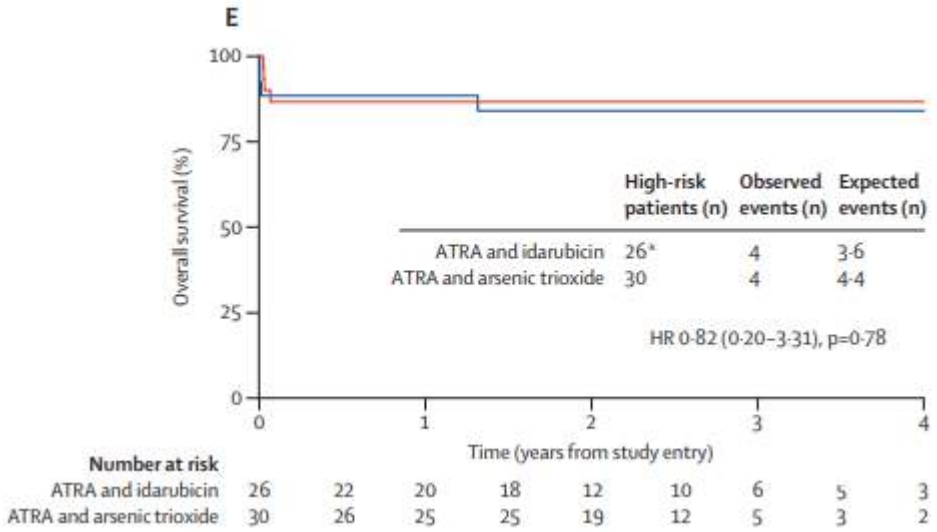




ATRA and ATO without CHT or GO was effective and safe for all-risk APL, suggesting that chemotherapy may be unnecessary for high-risk patients

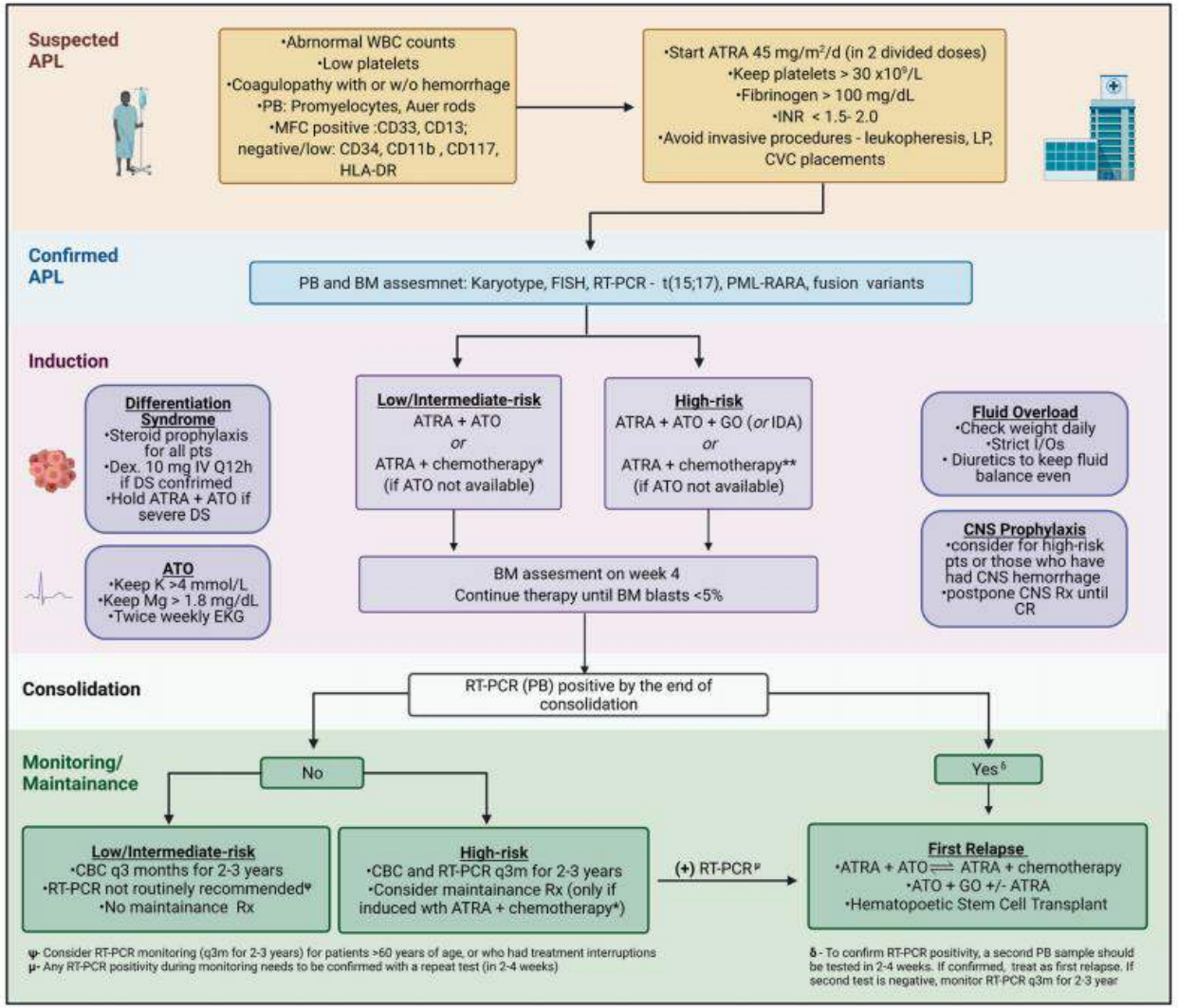
Wang et al Blood Cancer Journal (2022)

Arsenic trioxide and all-trans retinoic acid treatment for acute promyelocytic leukaemia in all risk groups (AML17): results of a randomised, controlled, phase 3 trial



ATRA and ATO is a feasible treatment in low-risk and high-risk patients with acute promyelocytic leukaemia, with a high cure rate and less relapse than, and survival not different to ATRA and idarubicin with a low incidence of liver toxicity.

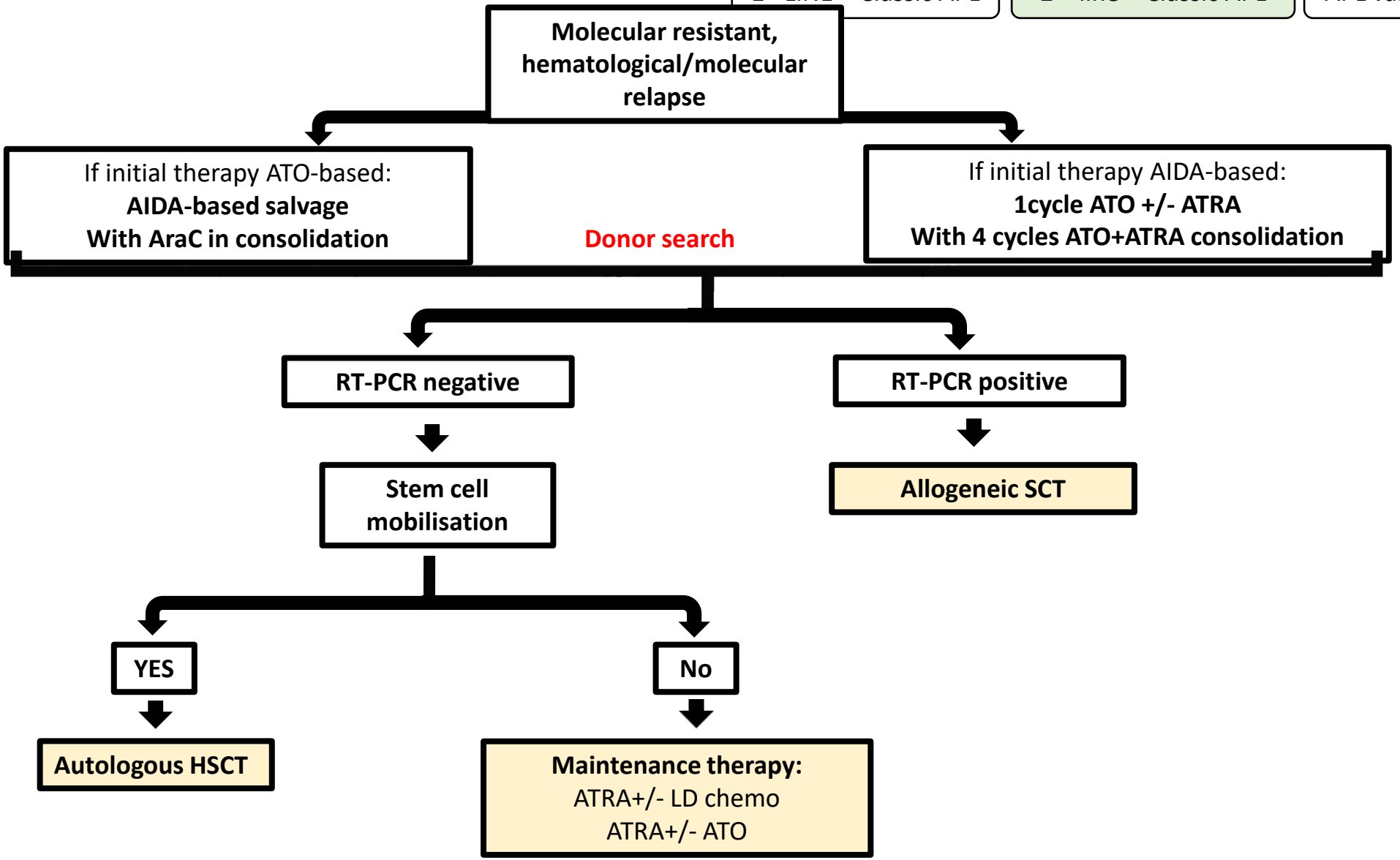
Burnett et al Lancet Onc 2015



- **<u>ATRA should be started as soon as APL is suspected</u>**
- Correct coagulation and avoid invasive procedures
- ATO or chemotherapy may be delayed until the genetic diagnosis is confirmed
- Confirm diagnosis with cytogenetic/molecular biology analysis
- Treat according to disease prognostic risk
- CNS prophylaxis in selected patients, **after the achievement of CR**

Yilmaz et al Blood Cancer Journal 2021

1st LINE – Classic APL | 2nd line – Classic APL | APL variant X-RARa



X-RARs fusions identified in APL: APL Variant

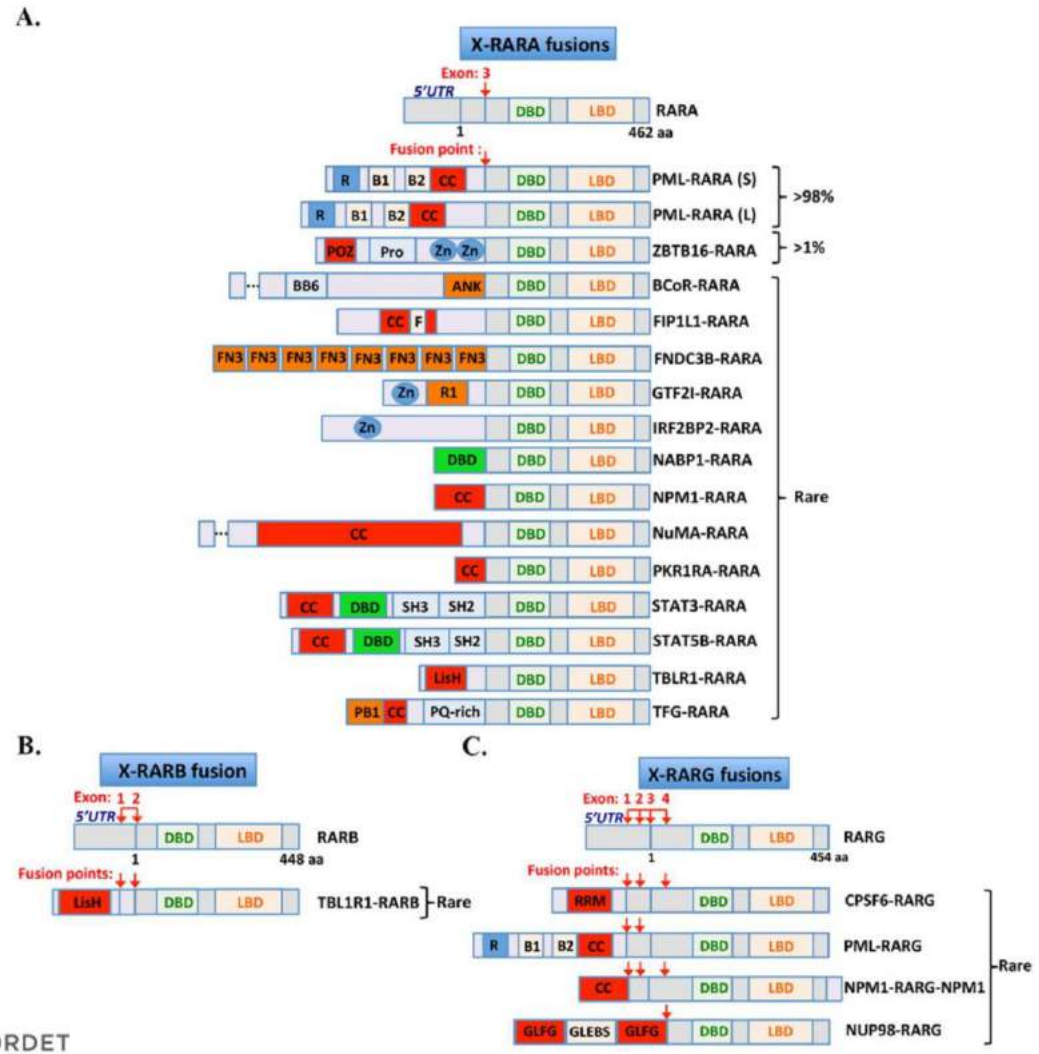


Table 2. ATRA/ATO therapy response for X-RARs fusions.

Fusion Protein	ATRA Response	ATO Response	Blast Decrease	Blast Differentiation	Self-Renewal of Bone Marrow
X-RARA					
PML-RARA	Sensitive	Sensitive	Yes	Yes	Yes
ZBTB16-RARA *	Resistant	Resistant	Yes	Yes	No
BCoR-RARA	Resistant	Resistant	ND	Yes [a]	ND
FIP1L1-RARA	Sensitive [a]	ND	Yes [a]	Yes [a]	Yes [a]
FNDC3B-RARA	Uncertain	ND	No	Yes [a]	No
GTF2I-RARA	Resistant	Resistant	No	No	No
IRF2BP2-RARA	Likely	Resistant	No	Yes [a]	Yes [a]
NABP1-RARA *	Uncertain	ND	No	Yes	ND
NPM1-RARA	Sensitive	ND	Yes	Yes	Yes
NuMA-RARA	Likely	ND	ND	Yes	ND
PRKAR1A-RARA	Uncertain	Uncertain	ND	Yes	ND
STAT3-RARA	Resistant	Resistant	No	No	ND
STAT5b-RARA	Resistant	Resistant	No	No	No
TBLR1-RARA	Resistant	Resistant	No	No	No
TFG-RARA	Sensitive	ND	Yes	ND	Yes
X-RARB					
TBLR1-RARB	Resistant	ND	No	No	No
X-RARG					
CPSF6-RARG	Resistant	Resistant	No	No	No
NPM1-RARG-NPM1	Resistant	Resistant	No	No	No
NUP98-RARG	Resistant	Resistant	No	No	No
PML-RARG	Resistant	ND	ND	No	ND

* ZBTB16-RARA (PLZF-RARA); NABP1-RARA (OBFC2A/RARA). ND: Non-determined; [a] (in 1 case). Uncertain: ATRA treatment combined with additional chemotherapy and/or stem cell transplantation.

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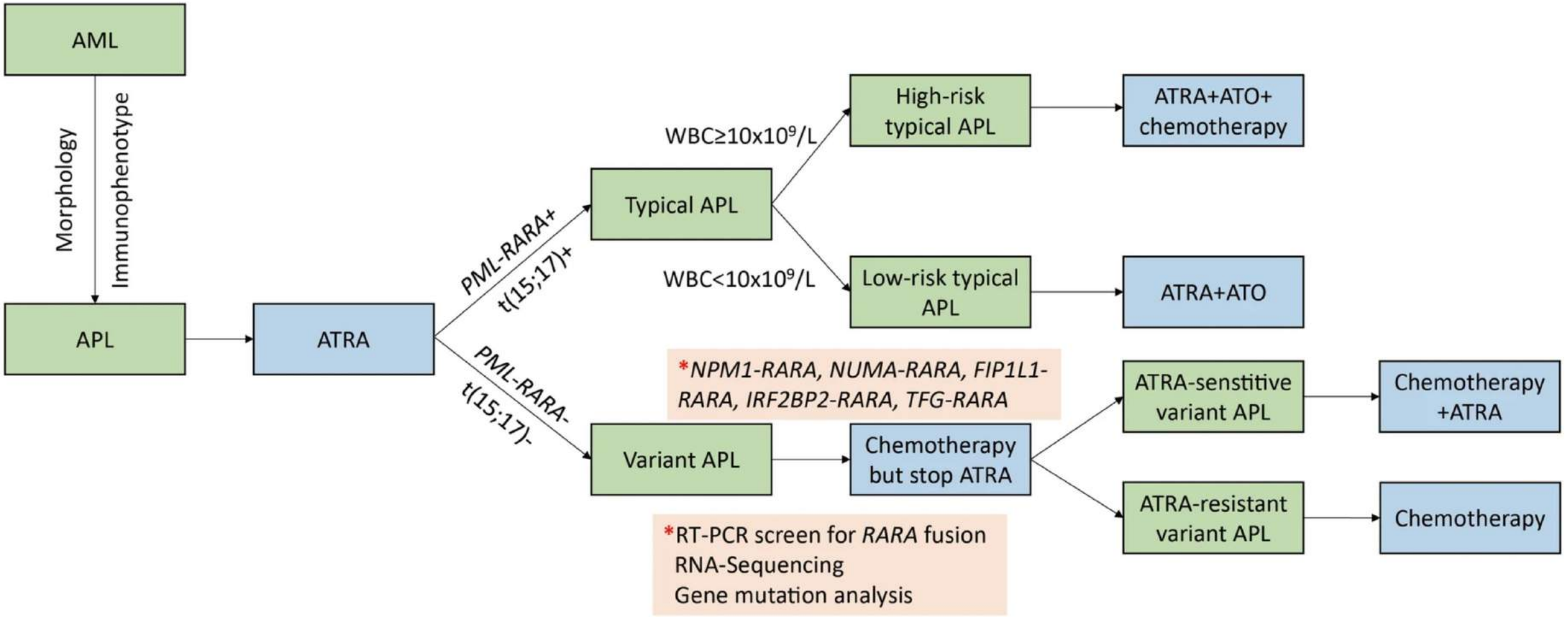
Hôpital Erasme ULB

1st LINE – Classic APL | 2nd line – Classic APL | APL variant X-RARa

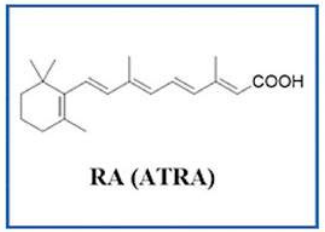


Zhang et al Biomarker Research 2021

Practical considerations

1. ATRA
2. ATO
3. Coagulopathy
4. Leukocytosis
5. Differentiation syndrome

ATRA



- Vitamine A- metabolite
- FAT soluble - Oral administration with meals.
- 45 mg/m2 in two equally divided doses.

- Leukocytosis, Differentiation syndrome, pseudotumor cerebri
- Common adverse events: fatigue, headache, fever, dermatitis, nasal stuffiness, hepatitis.

- Interactions: i.e. posaconazole

ATRA

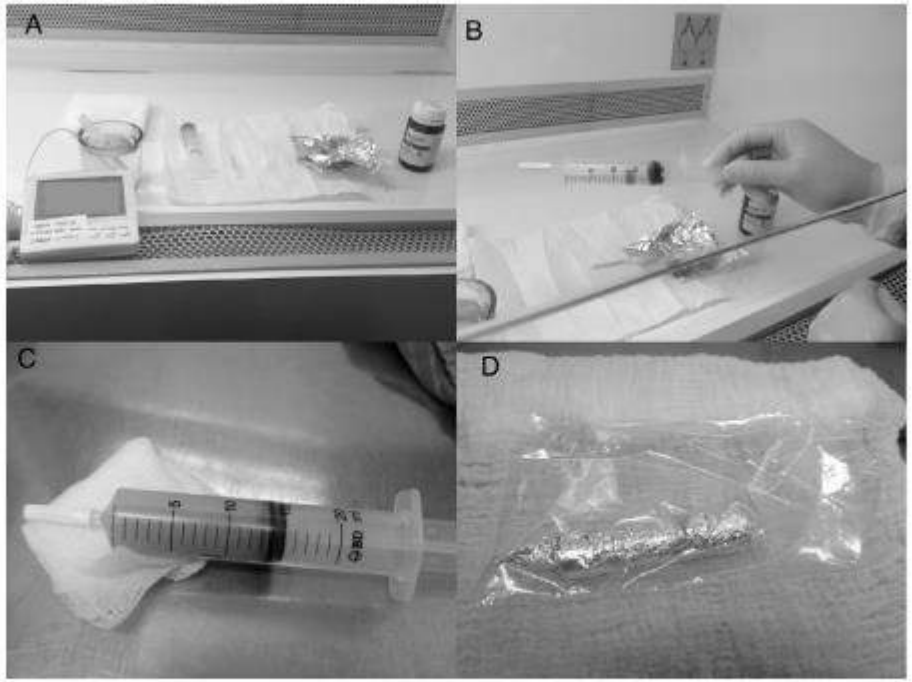
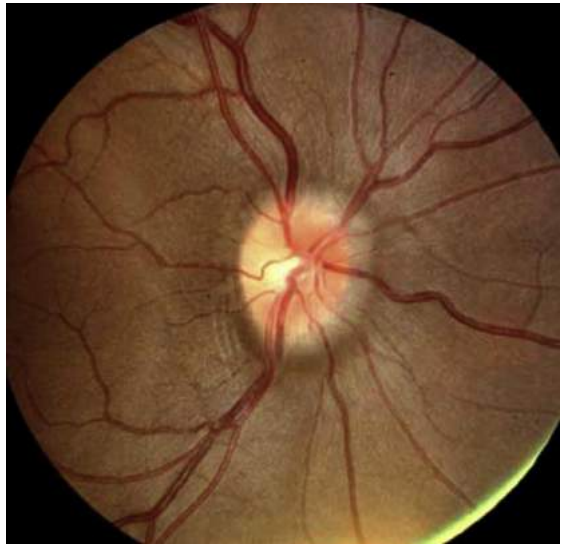


Figure 1 – Process to manipulate all-trans retinoic acid (ATRA). (A) Materials: gown, gloves, class II-B2 biological safety cabinet, thermometer, 20-mL syringe, luer lock or other available syringe/lock system, light protection (e.g.: aluminum foil or other effective system), distilled water heated to 40 °C and ATRA. (B) Syringe filled with 5–10 mL of heated distilled water with ATRA and air space for effective mixing. (C) Final product after vigorous shaking. (D) ATRA protected from the light.

Okumura Rev Bras Hem e Hemo 2017

Pseudotumor cerebri (ATRA)

Idiopathic intracranial hypertension
More common in children than adults
ATRA can induce the production of cerebrospinal fluid and inhibits its reabsorption
15% of pediatric patients



Clinical feature
Headache, papilledema, and/or vision loss.

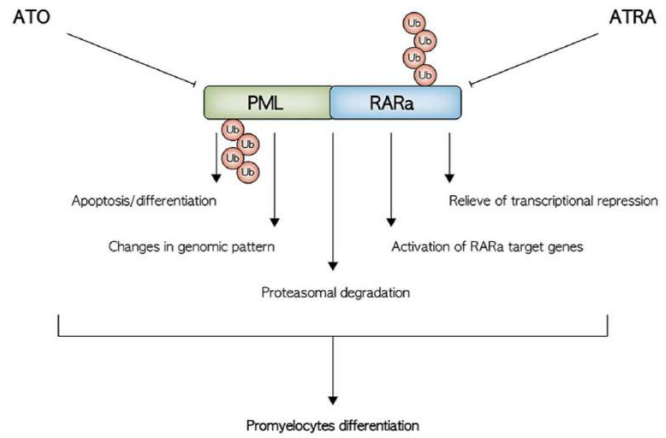
Elevated ICP
Normal CSF composition.
Negative CT/MRI
Papilledema is common

Treatment
Lumbar puncture
Temporary discontinuation ATRA, steroids, Acetazolamide

Coombs et al Clin Lymphoma Myeloma Leuk. 2017
Wall Neurologic clinics 2010

ATO

- 0.15 mg/Kg IV over 2 hours in induction
- Peripheral line
- Oral formulation available in China
- ATO should be restricted to cases confirmed to be PML/RARA



- Adverse events: QT prolongation, Leukocytosis, Differentiation Syndrome, hepatitis, neuropathy

Zhu et al Lancet Oncol 2018

ATO

- QTc monitoring and adaptation according to protocol

  >450 msec for men and >460 msec for women : stop ATO and other QT prolonging drugs.

Once QTc normalized, resume ATO at 50% dose for the first 7 days, and then if no further prolongation occurred progressively escalate to standard dose in two weeks.

DON'T USE BAZETT FORMULA

Bazett correction tends to overestimate true corrected QT

- Eletrolytic disturbances: keep the serum potassium > 4.0 mEq/L and serum magnesium > 0.8 mmol/l
- Pay attention to drugs that can prolong QT- posaconazole; ondasentron; fluoroquinolones…..

Coagulopathy

- Start ATRA (ATRA downregulates both TF and CP, highly expressed by APL blasts)
- Fibrinogen/platelets/fresh frozen plasma to maintain:

  Fibrinogen> 100-150 mg/dl

  Platelets > 30000-50000/mcl

  INR< 1.5
- Heparin, tranexamic acid → No benefit
- Avoid invasive procedures due to bleeding risk (lumbar puncture, central venous line placement...)
- Monitor coagulation until normalisation

Sanz et al Blood 2019
Falanga et al Blood 1998

Leukocytosis

- Cytoreductive chemotherapy should be started without delay

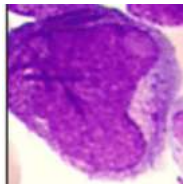
- Possibilities:

  - idarubicin or daunorubicin alone or combined with cytarabine
  - GO
  - Hydroxycarbamide

- Leukapheresis should be avoided due to risk of precipitating fatal hemorrhage
- Prophylactic corticosteroids can be given, which may reduce the risk of APL differentiation syndrome

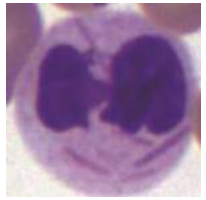
  Methylprednisolone 0.5 mg/kg

Differentiation syndrome



APL Promyelocytes

ATRA/ATO



Cytokine release – Endothelial damage
Adhesion and tissue infiltration by neutrophils

Clinical features

Fever ≥ 38° C
Weight gain > 5 kg
Hypotension
Dyspnoea
Radiographic opacities
Pleural or pericardial effusion
Acute renal failure

Grading of DS severity:
Severe: ≥ 4 features
Moderate: 3 features
Indeterminate: 1–2 features

Treatment of presumed APL DS:

Start empiric treatment
Dexamethasone 10 mg every 12 h
If no improvement within 24 h: increase frequency to every 6 h
Stop/taper once complete relief of signs/symptoms

+

What to do with ATRA/ATO?
Hold: if severe DS OR no response to dexamethasone OR organ failure present and admission to ICU needed
Restart: once severe DS AND any organ failure resolved

+

Aggressive supportive care measures
(based on clinical features present)
Oxygenation/mechanical ventilation
Fluid management/renal replacement therapy
Management of coagulopathy

+

Rule out "mimickers" AND consider empiric treatment
(based on clinical features present)
Infection/Sepsis
Pulmonary embolus
Diffuse alveolar haemorrhage
Congestive heart failure
Anaphylactic reaction to drugs
Other causes of acute renal failure

- 25% of patients
- Associated with high white blood cells, poor PS and hypoalbuminemia
- An increase of WBC levels above 10000 /mcl after treatment initiation with ATRA and/or ATO should be interpreted as a sign of ATRA/ATO-induced differentiation and **should not lead to reclassification of the patient as having high-risk disease**

Take Home Messages

- APL is a medical emergency
- If you suspect APL, ask for PML/RARα FISH/PCR and START ATRA
- Treat coagulopathy aggressively and avoid invasive procedures
- Chemo-free approach SOC in non high risk patients and in high risk?
- Morphological variant (macro versus microgranular) ≠ Molecular variant (X-RARα)
- Special adverse events with ATRA ATO to be aware of

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