Stroke in isolated mlecular relapse in acute promyelocytic leukemia(APL)

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CASE presentation (1)

- a 7-year-old boy with APL was periodically evaluated for BMA/B during maintenance therapy witht **t(15,17)/PML-RARA transcript.**
- **BMA:**no abnormal morphologic changes ,
- **PML-RARA transcript** was positive in BM.
-
- BMA was repeated **2 weeks** later t (15,17) again was positive without any evidence of **morphological recurrence** in the BM.
- FLT3-ITD :neg
- After 3 weeks of delay in admission (due to clincal symptoms of COVID-19) he was hospitalized for **right hemiparesis** and **speech disorder**.

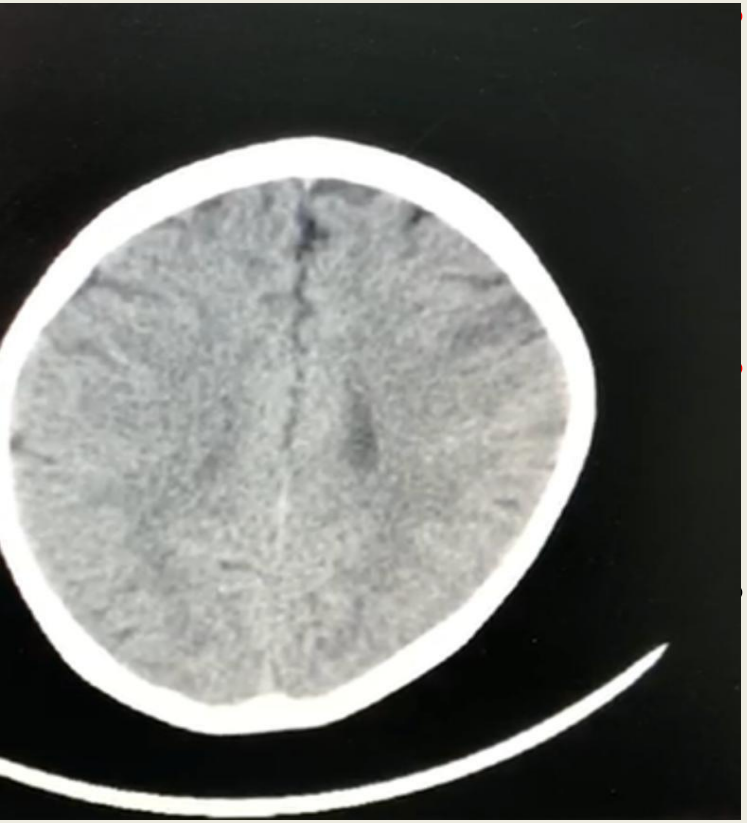
Ph/E:

- LOC(-) , slurrede speech (+)
- Neurologic exam :right hand paresia with 1/5 & right leg with 3/5 motor power
- Sensory loss(-)
- DTR:
- right bicepes:dec
- knee:dec
- Plantar:downward
- After initiation of **DEXA & Enoxa** speech & paraparesia corrected after 3 days.

Laboratory TESTS:

- WBC =2700 (N = 48, L = 52), Hb =12.2 platelet = 273000.
- PT and PT / INR were normal
- **D-Dimer =4732** micrograms per liter.
- Fibrinogen: Normal
- LDH: Normal
- Other biochemical tests were normal.

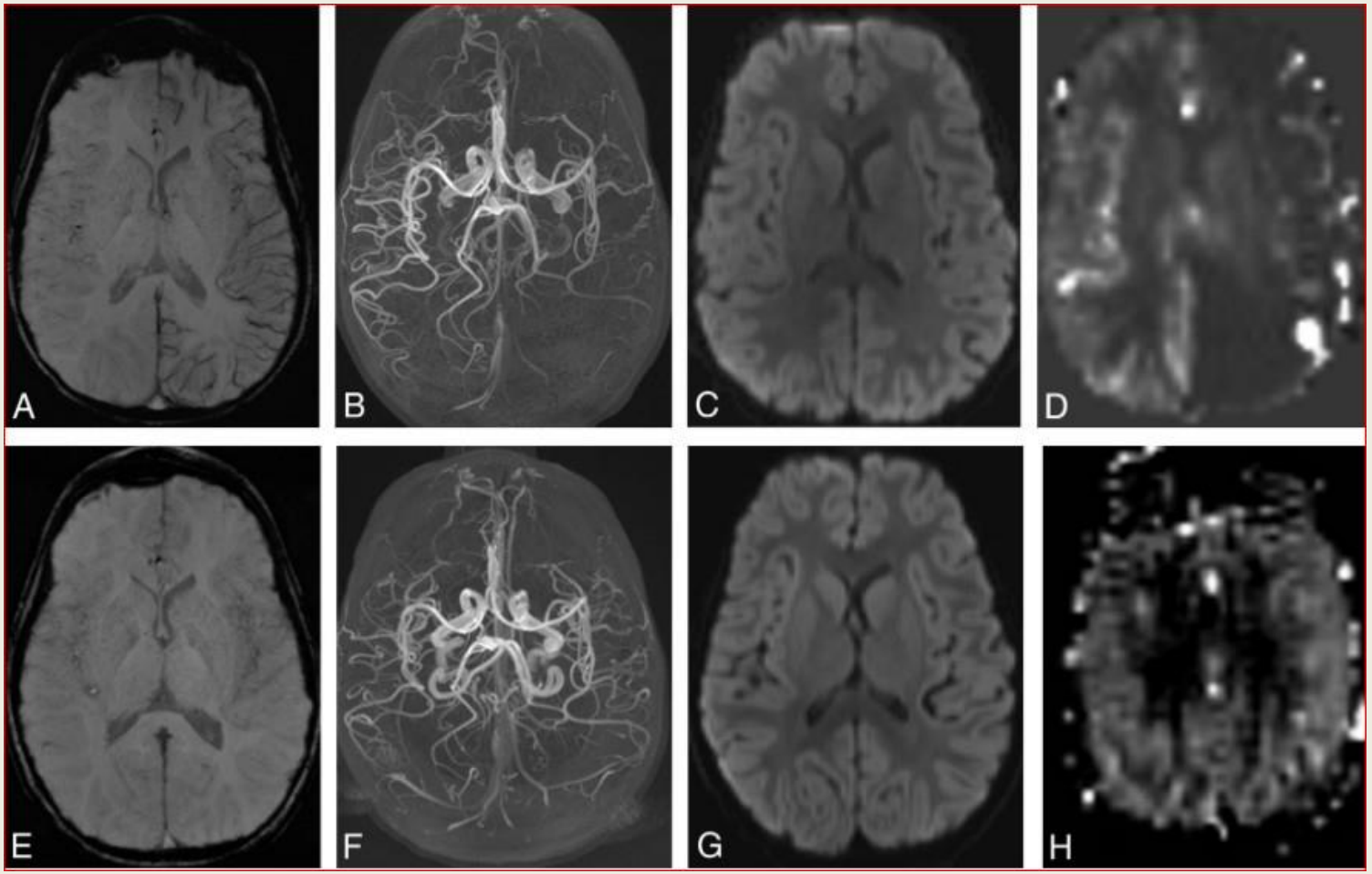
Brain imaging:



Brain CT : a new ill-defined hypodencity in the **left region** of the middle cerebral artery(MCA)as a stroke like area.

Brain MRI and MR angiography (MRA) and DWI:

Hypoperfusion in **left hemisphere**, asymmetric venous bulge insensitive weight imaging, and pruning of the left hemisphere peripheral arteries on MR angiography.


A
B
C
D
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Patient management:

- 1.**Dexamethasone** 2 mg tds daily until slurred speech and hand paresia resolved then 2 days in week.(**diffrentiation syndrome** prophylaxis)

- 2.**LMWH** subcutaneous (Enoxaparin 2.000 IU. q12h)
- 3.**ATO**(0.15 mg/kg/d IV for 35 days)
-
- 4.**ATRA** 20 mg / m2/d(ECHO/ daily **QTc** +ca,p,mg,Na,k/**Inderal**)
- 5.Idarubicin 12 mg/m2 on day 1,3,5

- 6.**ASA**:after discharge and enoxa discontinuation (between 2 ATO courses)
-

Patient novelty:

- ***1.Isolated molecular relapse with non-hematologic clinical presentation***
- ***2.rare prevalence***
- ***3.Clinical thrombosis+subclinical fibrinolysis***

Thrombosis & hemorrhage in APL

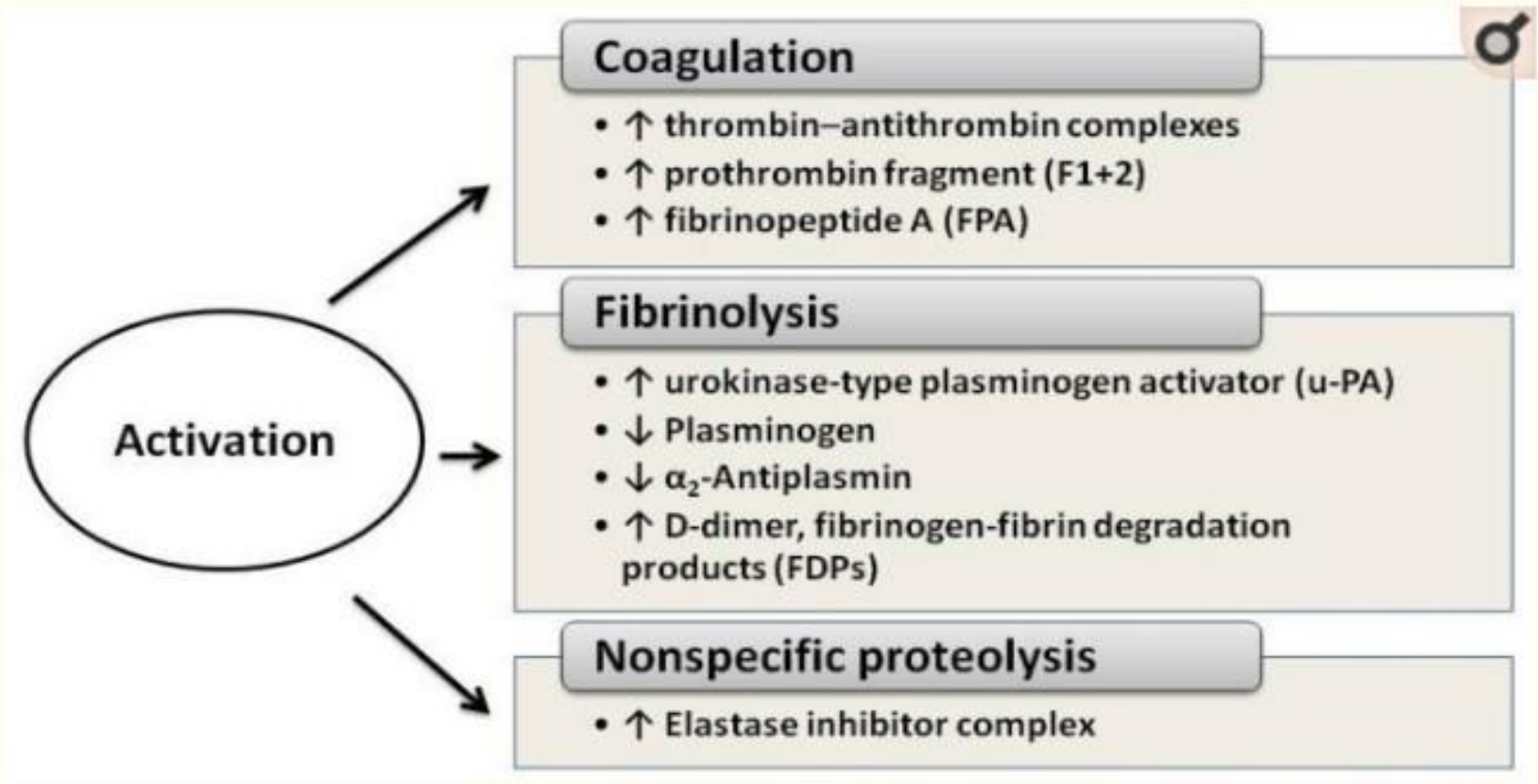

Figure 1

Laboratories abnormalities of hemostasis in APL patients.

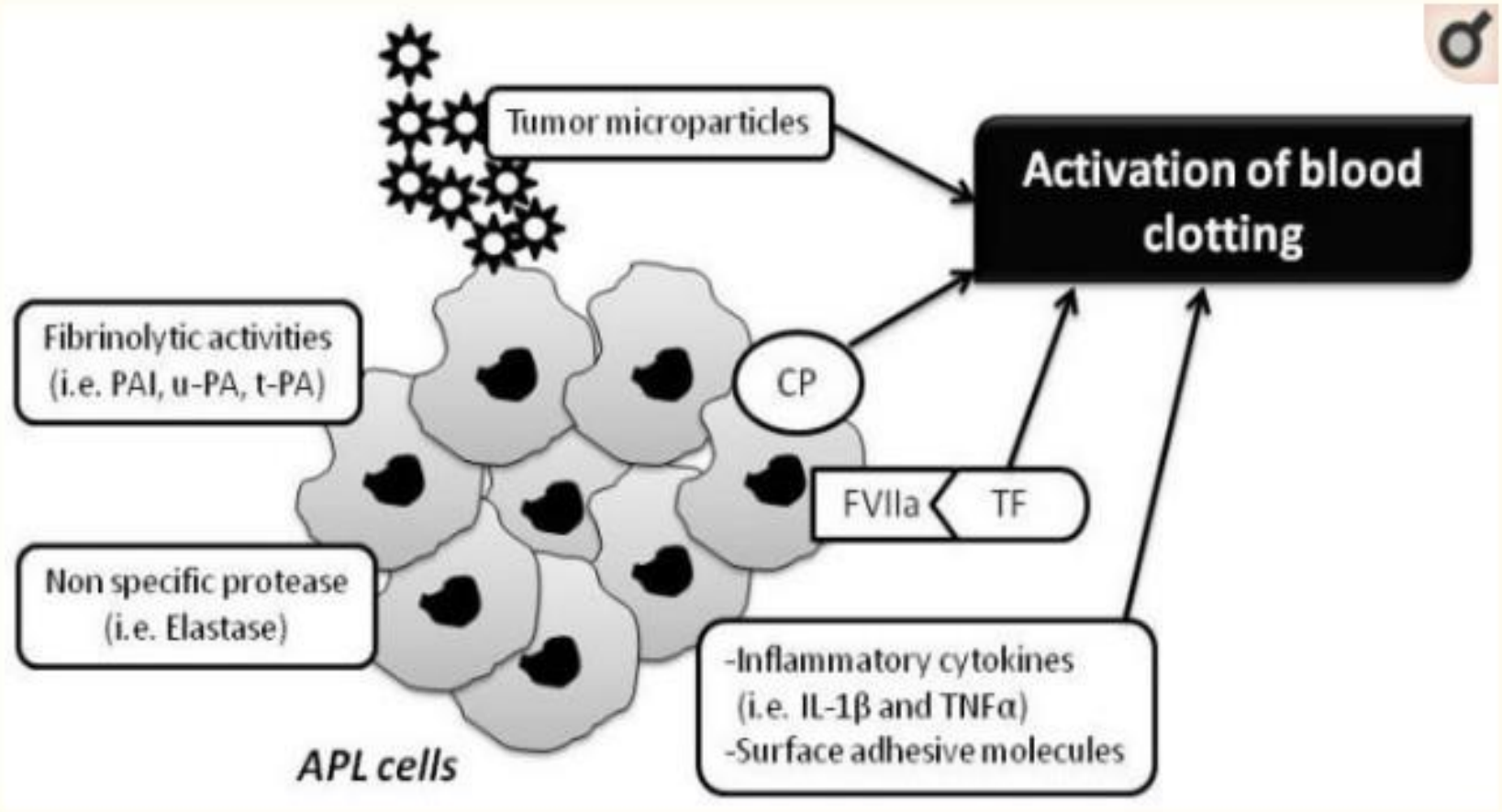

Figure 2

Procoagulant mechanisms of APL cells.

Critical points:

- ***1.D-dimer:H,fibrinogen:L***-→co-activation of thrombosis & fibrinolysis→DIC/hemorrhagia

- ***2.D-dimer:H,fibrinogen:N***-→fixed thrombosis/ischemia & then fibrinolysis

- 3.**MRD** monitoring in BM/PB is considered BY t(15,17) or **PML-RARA transcript** in APL ***every 3 months for 3 years.***
- (Although **peripheral blood** (PB) PCR has good concordance with **BM** PCR at early stages of therapy, have shown an advantage for BM PCR **after consolidation**, with 1-5 log greater **sensitivity** than PB.)
-

- 3) **Chemotherapy** in isolated molecular relapse without any evidence of hematologic relapse is necessary, because isolated molecular relapse in APL is **equal positive minimal residual disease(MRD)** and need treatment intensification include **reinduction** with differentiating agents + chemotherapy & **consolidation** with differentiating agents +_allogenic stem cell transplant**(SCT).**

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The Epidemiology and Clinical Associations of Stroke in Patients With Acute Myeloid Leukemia: A Review of 10,972 Admissions From the 2012 National Inpatient Sample

Christopher Del Prete,[1] Taeha Kim,[1] Frederick Lansigan,[2] Joseph Shatzel,[3] Harley Friedman[1]

Abstract

Acute leukemia predisposes patients toward the development of stroke. The latter, although devastating clinically, has been infrequently studied. Our study, using the 2012 National Inpatient Sample, found a 50-fold increase in the risk of stroke as compared with all inpatient admissions with a corresponding 5.5-fold increased risk of mortality. Significant risk factors for the development of stroke included urinary tract infection, hypernatremia, and acute renal failure.

Background: Acute leukemia is known to confer an elevated risk of both hemorrhagic and thrombotic complications, but the development of stroke in this population is poorly characterized. This study assesses clinical and epidemiologic factors in a population of inpatients with acute myeloid leukemia (AML) and stroke. **Methods:** Using the 2012 National Inpatient Sample, demographic and clinical data including age, gender, race, length of stay, in-hospital procedures, discharge diagnosis, disposition, and mortality incidence were extracted. **Results:** Of 7,296,968 admissions, 10,984 patients with active AML were analyzed. Of these, 65 patients had a concomitant cerebrovascular accident (CVA) (hemorrhagic or ischemic). There was a 50-fold increase in the risk of stroke in patients with active AML compared with all admissions. Patients with AML and CVAs were found to have significantly higher inpatient mortality than for all admitted patients with stroke (36.9% vs. 6.7%; odds ratio, 5.5; 95% confidence interval, 2.3-8.8; $P < .0001$). Multivariate logistic regression, after controlling for confounding variables, identified acute renal failure with tubular necrosis, hypernatremia, urinary tract infection, and secondary thrombocytopenia as significant predictors of stroke. **Conclusions:** Patients with AML have an elevated risk of CVA compared with all inpatients, and mortality in this population is high. Better characterization of risk factors of stroke in this vulnerable population is still needed.

Stroke in AML- 2017

Prevalence 6%

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Conclusions: Patients with AML have an elevated risk of CVA compared with all inpatients, and mortality in this population is high. Better characterization of risk factors of stroke in this vulnerable population is still needed.

Similar case :

Cardiovascular & Haematological Disorders-Drug Targets, 2010, *10*, 1-6

A Case of Ischemic Stroke in Acute Promyelocytic Leukemia at Initial Presentation: Relevance of All-Trans Retinoic Acid Treatment

Angelo M. Carella[1,*], Giuseppe Antonucci[1], Matteo Conte[1], Michele Di Pumpo[1], Elisabetta Antonucci[1] and Ernestina Ponziano[2]

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Abstract: Acute promyelocytic leukemia (APL) is frequently associated, often from the earliest phases, with a life-threatening coagulation/bleeding syndrome; disseminated intravascular coagulation (DIC) is described in majority of patients. We report a case of 49-year-old male, without cardiovascular risk factors, who suddenly developed ischemic stroke and splenic infarction as presenting symptoms of APL and related DIC. The patient was immediately treated with all-trans retinoic acid (ATRA) and the alterations of hemocoagulation parameters promptly returned in normal range. The coagulation/bleeding syndrome of the onset of APL is associated with high mortality; both diagnostic and therapeutic approaches require special and timely consideration of this condition. Treatment with ATRA is essential.

Key Words: Acute promyelocytic leukemia, Disseminated intravascular coagulation, Ischemic stroke, All-trans retinoic acid.

Table I. Poor Prognostic factors in paediatric relapsed APL

Relapse <18 months from diagnosis* (Marjerrison *et al*, 2014)
CR1 <18 months† (Lengfelder *et al*, 2015) and <12 months† (Chakrabarty *et al*, 2014)
Prior ATO therapy (Lou *et al*, 2014)
Positive MRD at HSCT or after consolidation (Lengfelder *et al*, 2015)
HSCT in ≥CR3 (Ramadan *et al*, 2012)
Positive MRD post-HSCT (Roman *et al*, 1997)
Absence of HSCT (Lengfelder *et al*, 2015)

CR, complete remission; ATO, arsenic trioxide; MRD, minimal residual disease; HSCT, haematopoietic stem cell transplant.
*Data in children only.
†Data in adults and children.

Table II. Proposed Risk classification of relapsed paediatric APL

Standard Risk
ATO-naïve and late relapse (18–36 months from initial diagnosis) with clearance of *PML-RARA* by PCR after 4 cycles of salvage therapy*, or
Very late relapse (>36 months from initial diagnosis), regardless of prior ATO exposure, with clearance of *PML-RARA* by PCR after 4 cycles of salvage therapy
ATO naïve and early relapse (<18 months from initial diagnosis) with clearance of *PML-RARA* by PCR after 4 cycles of salvage therapy, or
Prior ATO therapy and late relapse (18–36 months from initial diagnosis), with clearance of *PML-RARA* by PCR after 4 cycles of salvage therapy, or
Isolated extra-medullary relapse
High Risk
Prior ATO therapy and early relapse (<18 months from initial diagnosis), or
≥2nd relapse, or
Primary refractory disease, or
Any patient with positive *PML-RARA* by PCR after 4 cycles of salvage therapy (regardless of prior ATO exposure or time to relapse)

ATO, arsenic trioxide; PCR, polymerase chain reaction.
*Salvage therapy cycles include: 1 re-induction cycle lasting minimum 28 days and 3 consolidation cycles lasting 36 days each.

APL relapse risk stratification

ATO experience in children APL

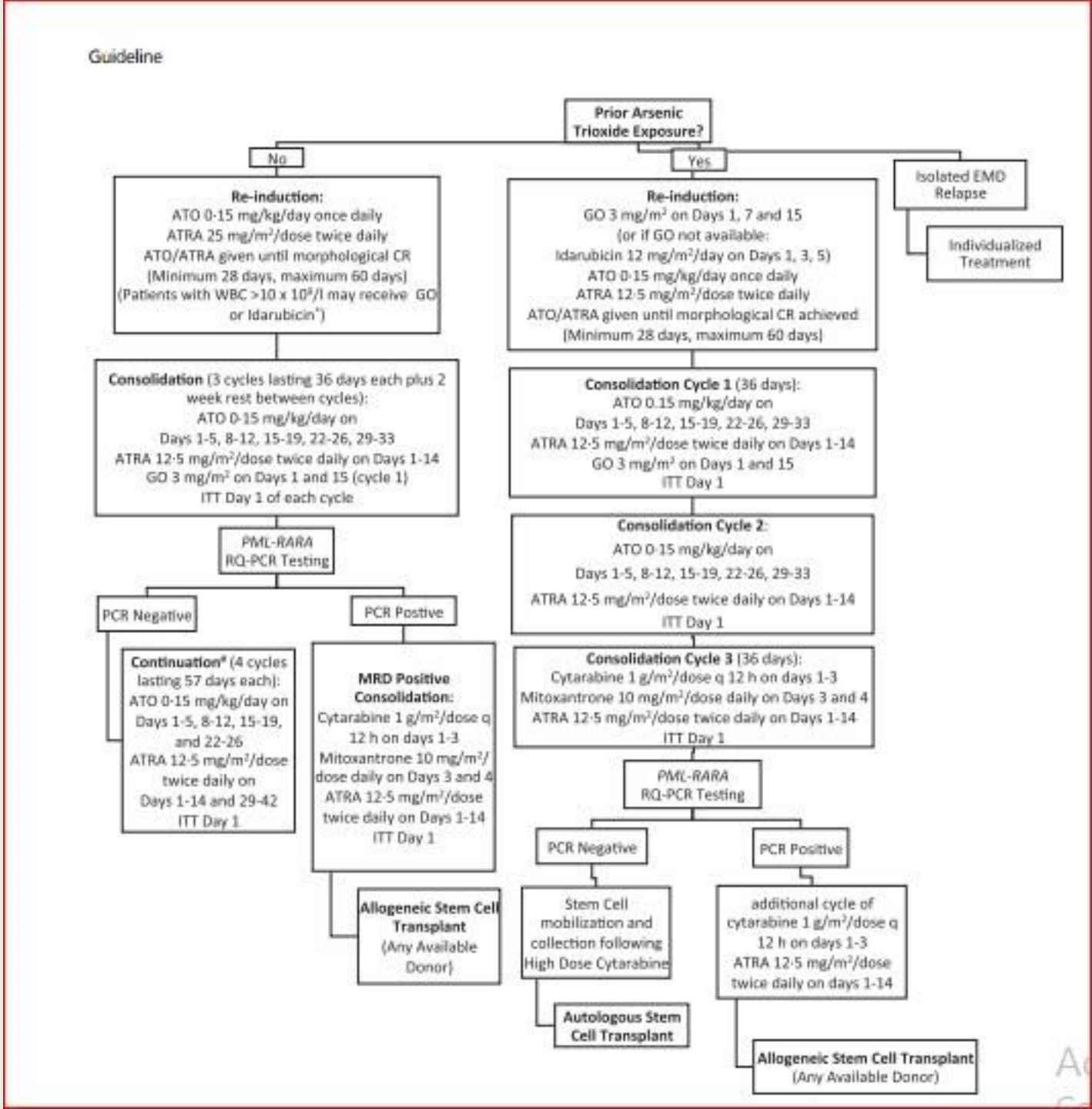
- **ATO, +_ATRA**, with relapsed APL (Ebinger et al**, 2011**; Au et al, 2012; Rock et al, **2014**).
- Au et al **(2012)** oral ATO/ATRA+ cytarabine/idarubicin+ Maintenance therapy included oral **ATO/ATRA** for 2 years

  ATO + ATRA in front-line therapy (Mathews et al, **2010**; Zhou et al, 2010 /Zhang et al, **2008**).
  relapsed/refractory APL **ATO**+**HSCT** (Fox et al,
  2008).

relapsed paediatric **APL ATO/ATRA + Chemotherapy / HSCT** (Zhang et al, 2008/Bally et al, **2012**).

- **Antracyclin/Ara-C+ATO+HSCT**; alive at 14–96 years from relapse (Creutzig et al, **2010**).

Treatment algorithm for relapsed pediatric APL that occurs 18–36 months from initial diagnosis in hematologic relapse.



blood

Review Article

Check for up

CME Article

The simpler, the better: oral arsenic for acute promyelocytic leukemia

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Arsenic trioxide and all-*trans* retinoic acid have become the frontline treatments for patients with acute promyelocytic leukemia (APL). Despite the long wait for an oral arsenic drug, a commercially available agent, realgar–indigo naturalis formula (RIF), was not launched in China until 2009. Since then, over 5000 APL patients have been treated with oral RIF in China. Oral arsenic not only shows a clinical efficacy comparable to that of IV formulations but also displays a better safety profile, improved quality of life, and lower medical costs for patients. The promising results promote incorporating an outpatient postremission therapy model into clinical practice for both low-risk and high-risk APL patients in China. In this review, we discuss the evolution of oral arsenic RIF in the treatment of APL, with a special focus on how to address the related complications during induction therapy. (*Blood*. 2019;134(7):597-605)

Our treatment plan:

- **RISK:standard risk with 1 poor prognostic factor**

- ***strategy:1:***
- 1.reinduction by ATO+ATRA+Ida+Ara-C
- **(PML-RARA transcript check)**
- 2.consolidation 1-→3courses **oral/IV ATO**+ATRA(25+12)
- 3.consolidation 1-→4courses **oral/IV ATO**+ATRA(25+12)
- ***(28+3x 36+4x57days=388-400 d)***

- ***strategy:2(traditional):***
- 1.reinduction by ATO+ATRA+Ida+Ara-C
- **(PML-RARA transcript check)**
- 2.consolidation 1-→1courses **IV ATO**+ATRA(25+12)+**BMT**

Take home message

- We recommend periodic **D-dimer,CBC diff,PT,PTT & PML-RARA transcript** ***every 3 months*** (detect hematologic/molecular recurrence).
- ***LMWH+_Cryo/plt*** base on thrombotic or fibrinolysis trend
- ***Antiplatlet agent /thrombolytic therapy*** are not recommended in APL

bjh guideline

Management of relapsed and refractory childhood acute promyelocytic leukaemia: recommendations from an international expert panel

Oussama Abla,[1] Matthew A. Kutny,[2] Anna Maria Testi,[3] James H. Feusner,[4] Ursula Creutzig,[5] John Gregory Jr,[6] Brenda Gibson,[7] Guy Leverger,[8] Raul C. Ribeiro,[9] Owen Smith,[10] Franco Locatelli[11,12] and Gertjan Kaspers[13,14]

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