



The Impact of Oral Arsenic and ATRA on Coagulopathy in APL

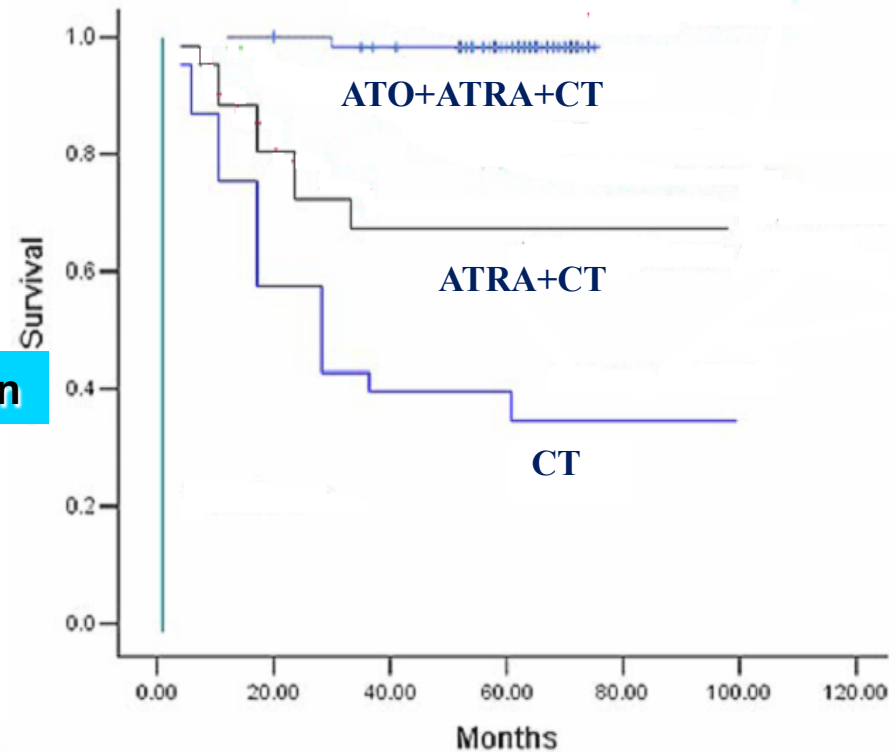
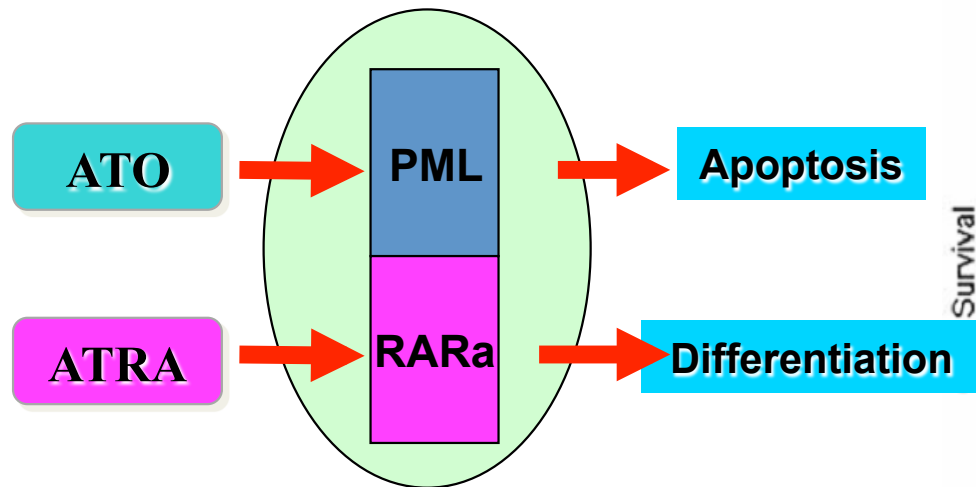
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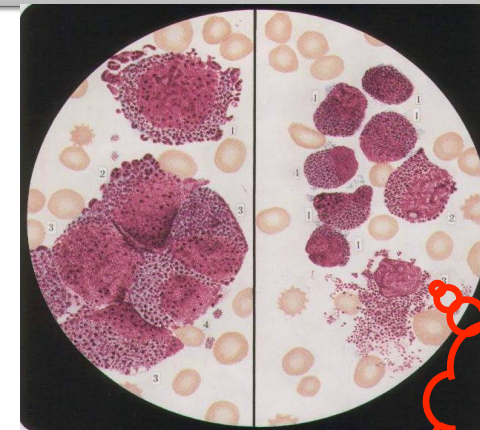
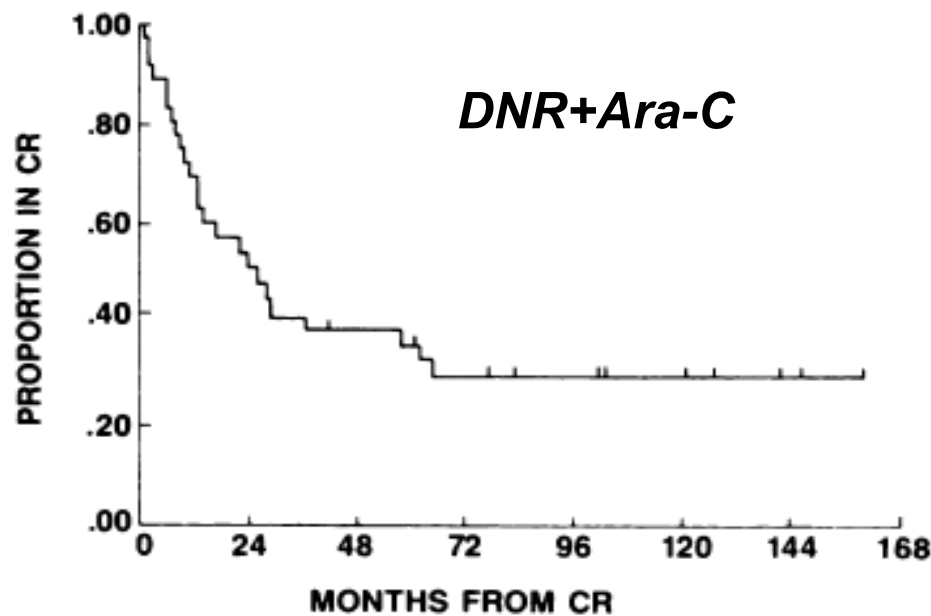
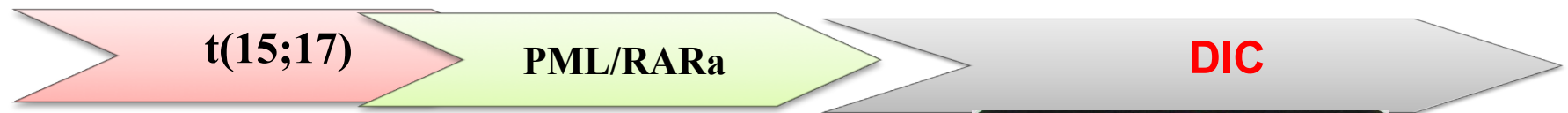
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APL is a highly curable disease in ATRA/ATO era



Chen SJ, et al. Blood 2011;117:6425

Coagulation abnormalities is fatal for APL

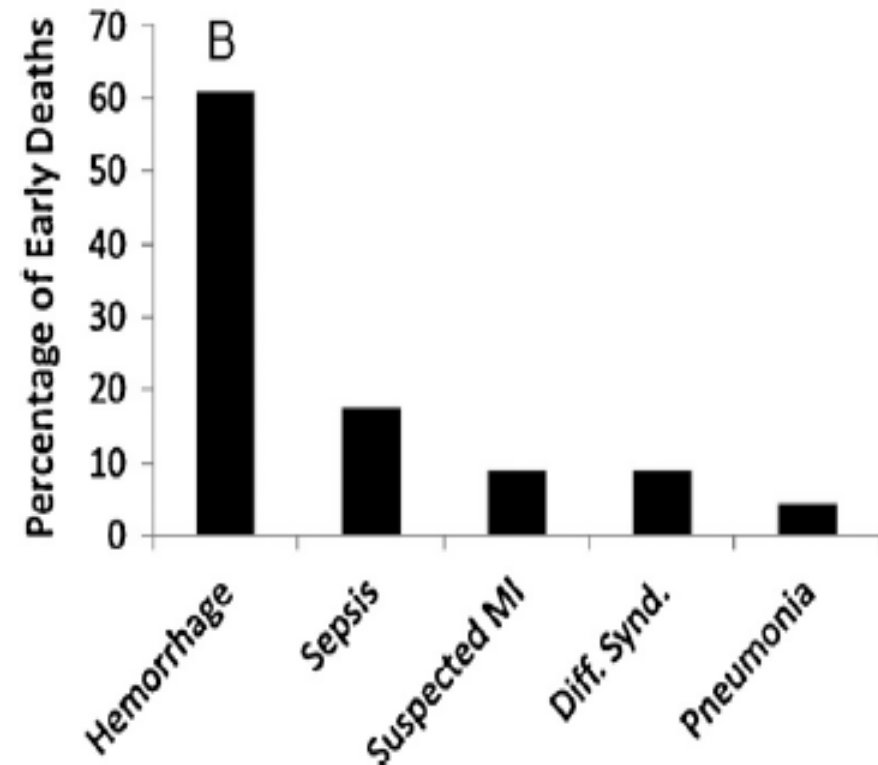
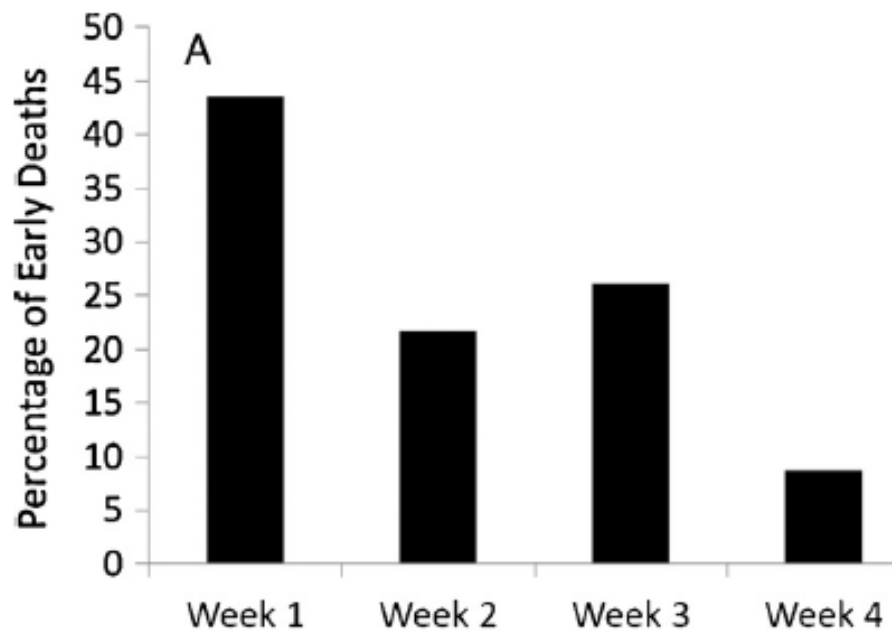


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I Cunningham, et al. Blood 1989 ;73:1116

Early death is 5-30% and majorly caused by hemorrhage



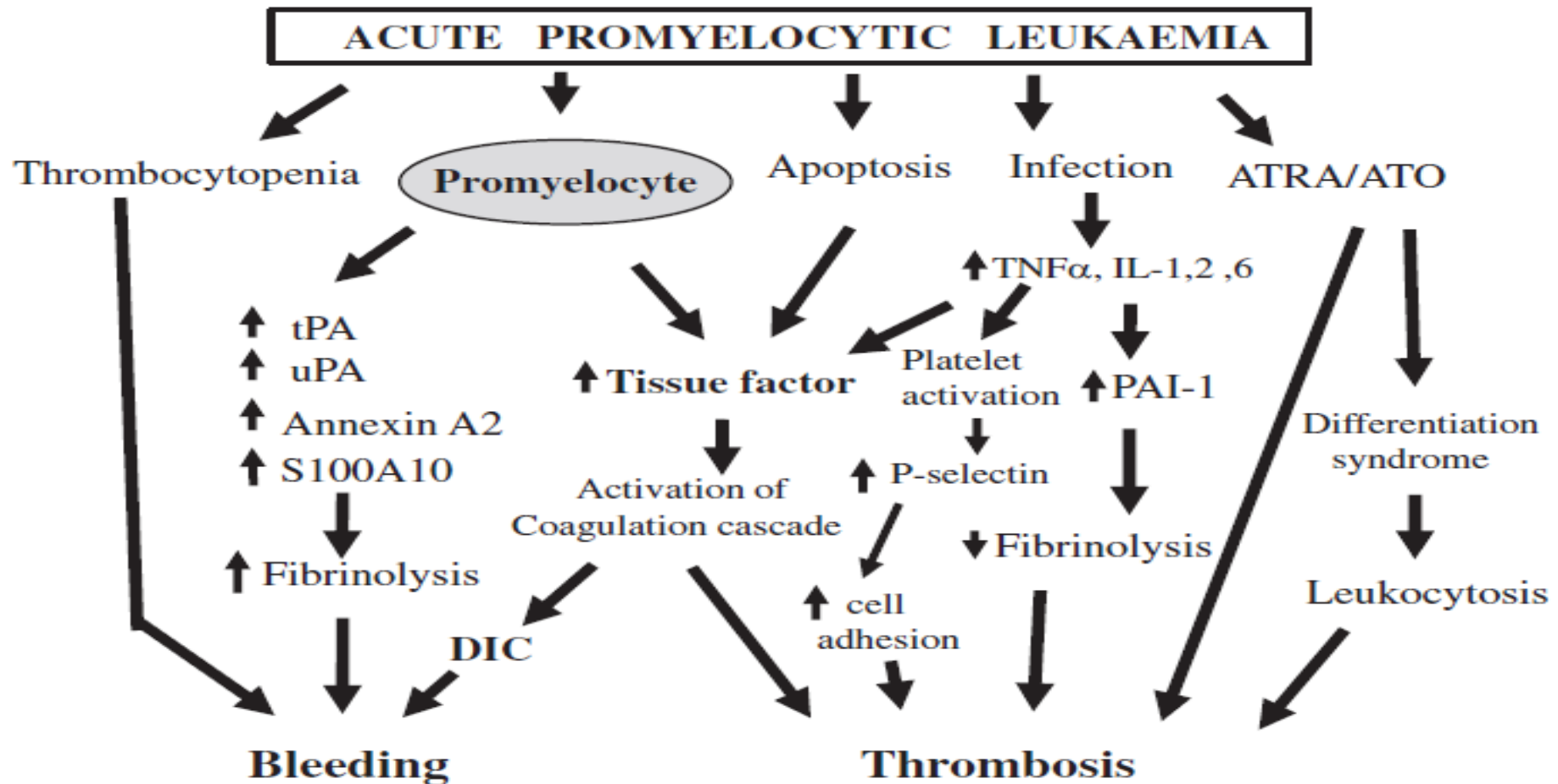
Incidence of Bleeding

Study	Incidence of ED	Incidence of bleeding amongst ED	Bleeding site	Risk factors
PETHEMA [13]	7%	69%	CNS Lung GI	Increased creatinine High blast count in PB Coagulopathy
Japanese [14]	5%	69%	CNS Lung	Lower fibrinogen High WBC Worse PS
GIMEMA [16]	3.8%	nr	CNS	High blast count in PB High hemorrhagic score
Swedish [19]	29%	41%	CNS	Increased creatinine High WBC High LDH High C-protein Low platelet count
Chicago [20]	11%	61%	CNS	High WBC count Lower fibrinogen Increased PT or PTT Delayed ATRA administration

Incidence of Thrombosis

Reference	Incidence	Risk factors
Ziegler et al [25]	6.5%	Nr
De Stefano et al [26]	9.6% (8.6% cumulative incidence at 6 mos)	Nr
Breccia et al [30]	8.8%	High WBC CD2/CD15+ FLT3-ITD+
Montesinos et al [36]	5.1%	Low fibrinogen M3 variant type
Rodriguez-Veiga et al [37]	4.1% at diagnosis (9.3% during induction)	High platelet count Hypoalbuminemia Male sex Worse PS

The mechanism of coagulation abnormality in APL



Question

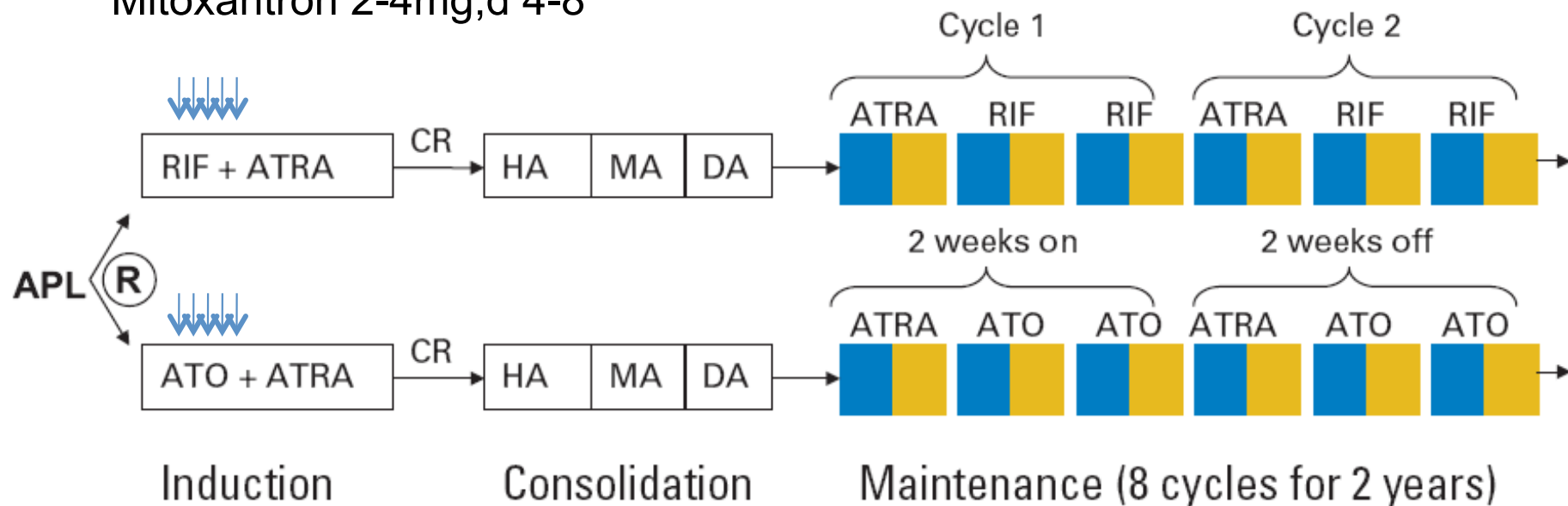
- Whether oral arsenic and ATRA can ameliorate coagulopathy in APL?
- Is there any difference of impact on coagulopathy between oral vs iv. arsenic

Purpose

- to evaluate the impact of oral arsenic (the realgar-indigo naturalis formula, RIF) + ATRA on coagulopathy in APL compared with intravenous ATO+ATRA during induction.

Methods

Mitoxantron 2-4mg,d 4-8



Hong-Hu Zhu , et al. JCO 2013; 31 : 4215

Results

- Period: 2007-2012
- 83 patients in our center(45 oral, 38 IV.)
- Hemostasis analysis during induction

Diagnostic Criteria of Disseminated Intravascular Coagulation

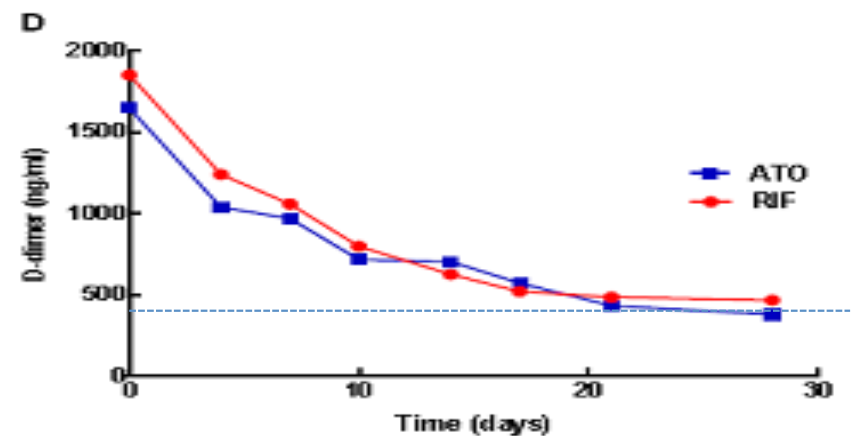
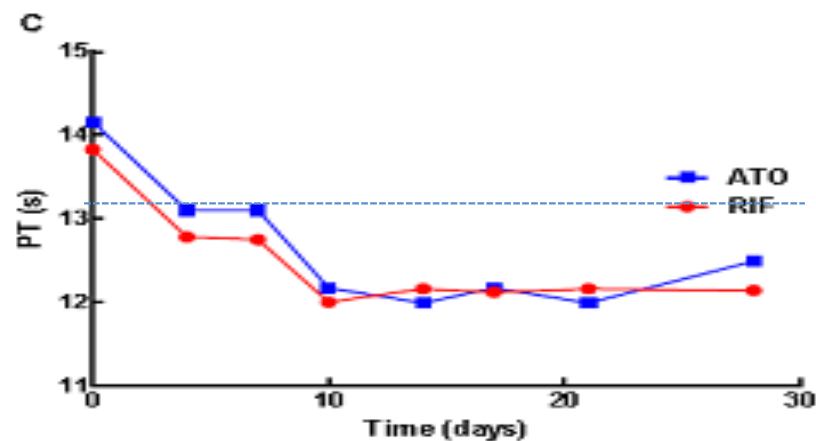
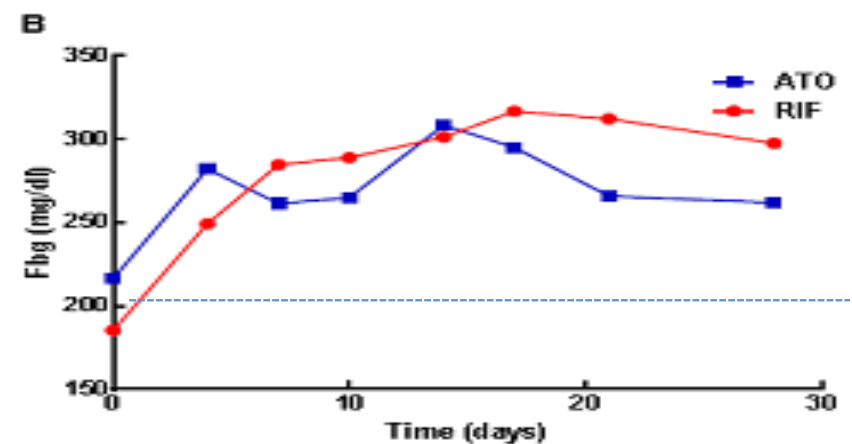
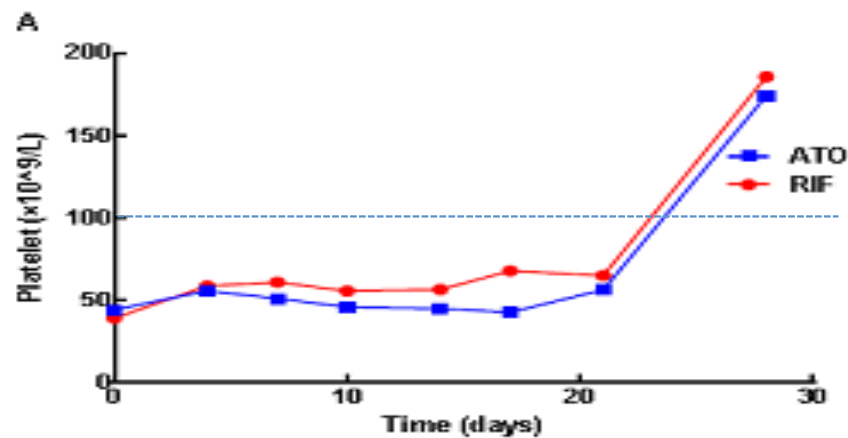
Overt-DIC criteria by the ISTH	
Underlying disease	0 points (essential)
Clinical symptoms	0 points
Platelet counts ($\times 10^3/\mu\text{L}$)	> 50 but < 100 ; 1 point, < 50 ; 2 points
Fibrin-related marker	FDP, D-dimer, SF moderate increase ; 2 points, strong increase ; 3 points
Fibrinogen (g/L)	< 1 ; 1 point
PT	Prolonged PT (sec) > 3 but < 6 ; 1 point > 6 ; 2 points
Diagnosis of DIC	≥ 5 points

Taylor FB, et al. Thrombosis and Haemostasis. 2001;86:1327-30

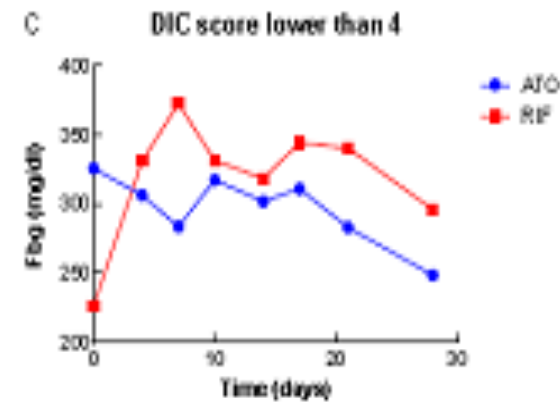
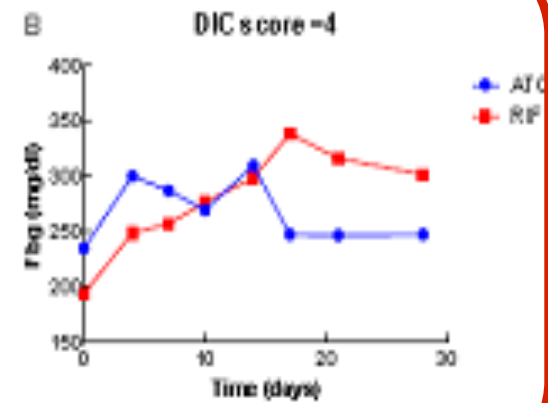
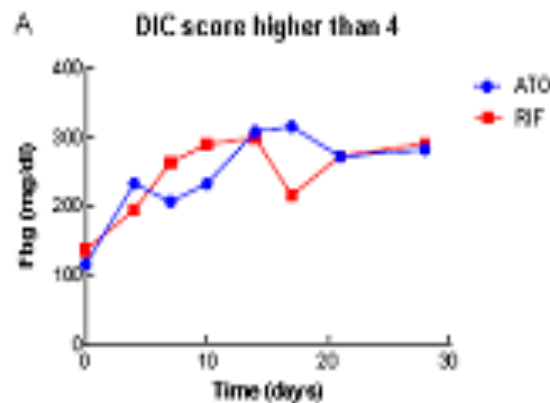
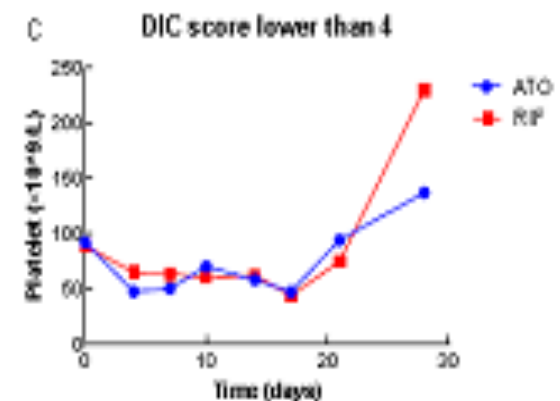
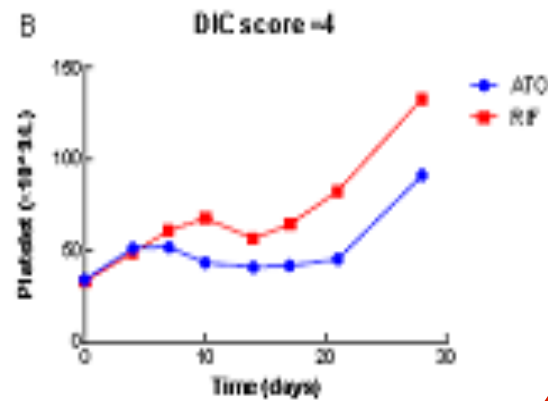
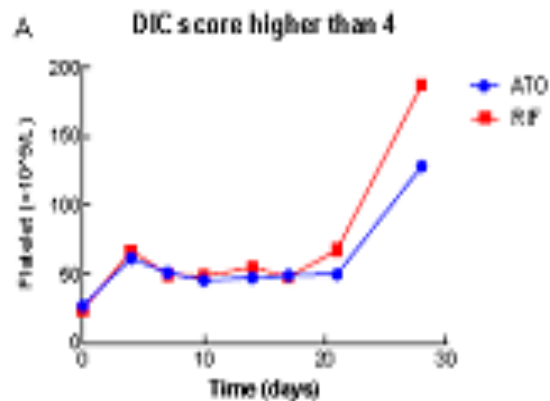
Characteristics of APL patients

Variable	Patients (n=83)	RIF (n=45)	ATO (n=38)
Age (years)	36 (15-59)	35 (15-59)	37 (15-59)
Gender			
Male	49	26	23
Female	34	19	15
White blood cell count ($\times 10^9/L$)	6.7 (0.31-45)	6.18 (0.6-34.6)	7.46 (0.31-45)
Hemoglobin level (g/L)	84.65 (45-154)	85 (45-141)	85.26 (48-154)
Platelet count ($\times 10^9/L$)	42.43 (7-164)	41.64 (7-139)	44.11 (10-164)
PT (s)	13.98 (10.6-20.1)	13.83 (10.6-18.7)	14.16 (11-20.1)
APTT (s)	28.61 (17.4-64.5)	29.26 (21.9-64.5)	27.95 (17.4-37)
Fibrinogen (mg/dl)	199.46 (42-575)	185.2 (42-433)	216.34 (49-575)
D-Dimer (ng/ml)	1746.11 (277-6607)	1853.13 (463-6607)	1648.26 (277-6503)
Myeloblasts as % of bone marrow	80.9 (19-96)	81 (39-96)	81.75 (19-95)
% of PML-RARA/ABL transcripts	48.58 (9.4-141.7)	50.97 (11.3-141.7)	45.7 (9.4-117.9)
Type of transcript	n=83	n=44	n=38
Long	55	29	25
Short	14	12	12
Variant	4	3	1
FLT3 internal tandem duplication mutations	n=69	n=39	n=30
Positive	10	4	6
Negative	59	35	24
Cytogenetic features			
Solo t(15;17) translocation	70	40	30
Additional abnormal translocation	13	5	8
Platelet infused (units)	4.36 (0-16)	4.2 (0-16)	4.55 (0-14)
Plasma infused (ml)	1207.23 (0-10800)	1164.44 (0-10800)	1257.89 (0-6400)
Platelet recovery time (days)	13 (0-29)	12 (0-24)	13 (0-29)
Coagulopathy recovery time (days)	3 (0-33)	3 (0-27)	2.5 (0-33)

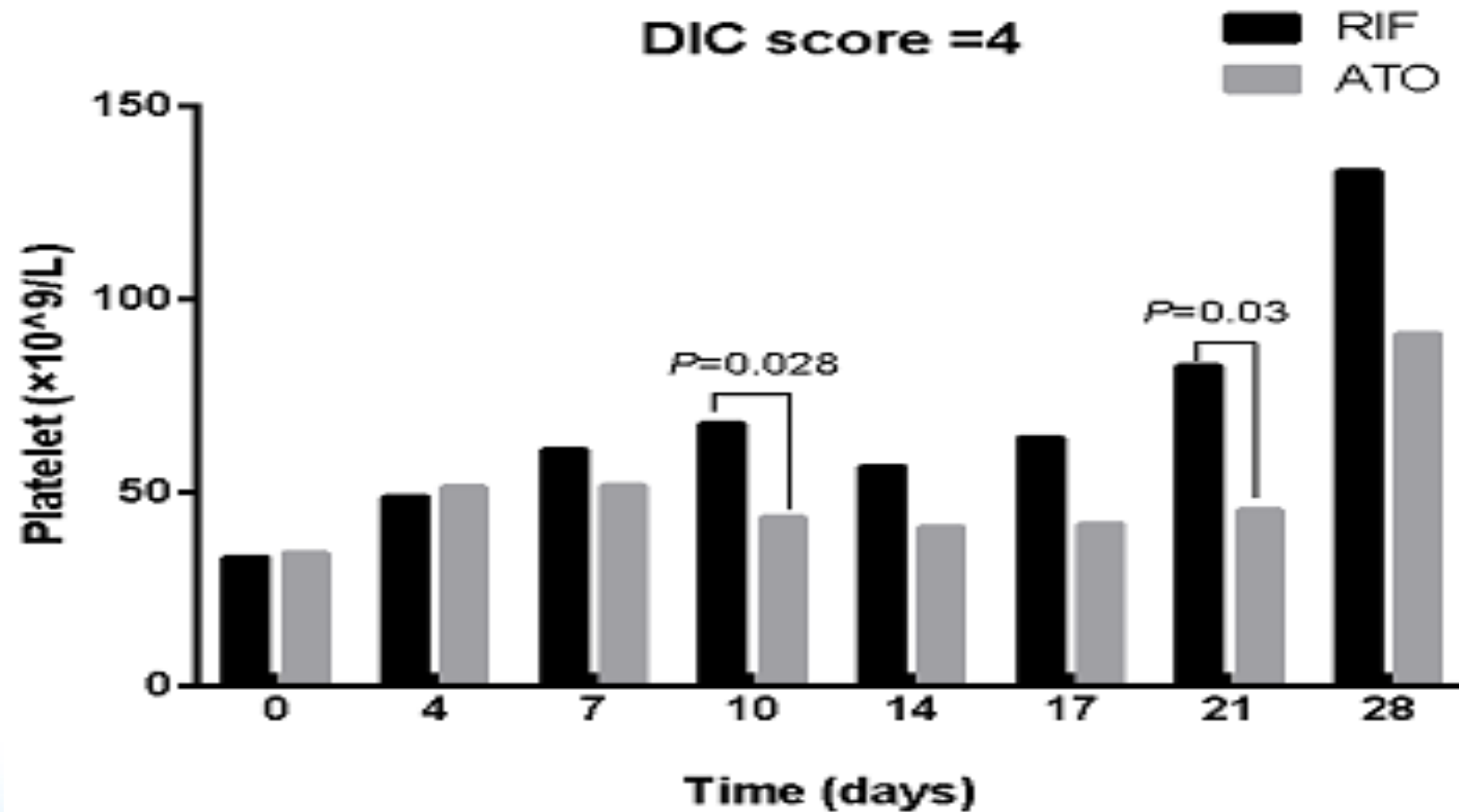
Comparison of the dynamic changes of hemostatic parameters between the RIF and ATO groups



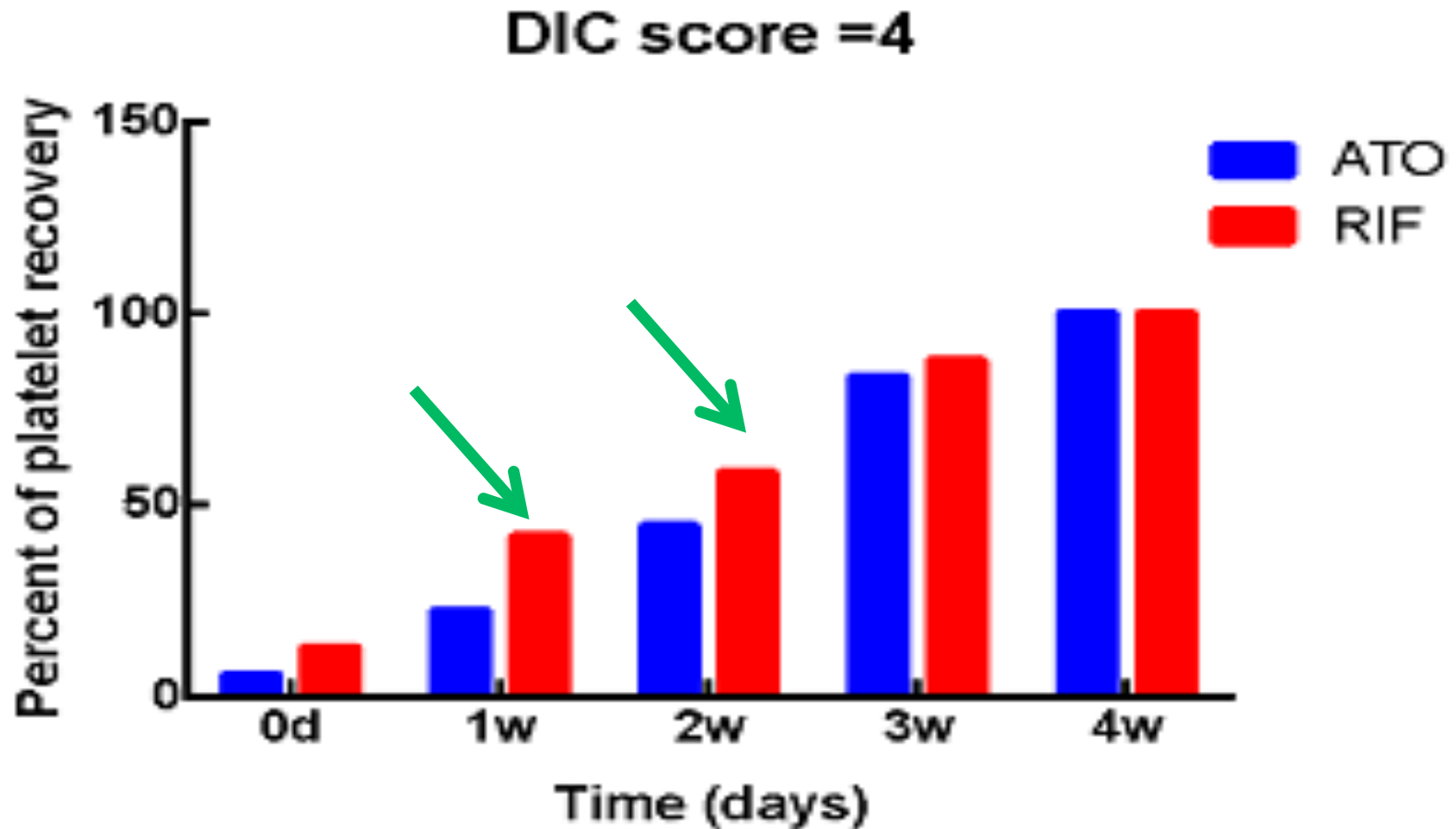
Comparison of the dynamic changes of hemostatic parameters in DIC Score=4



Platelet kinetics in DIC score=4



Platelet kinetics in DIC score=4



Conclusion

- RIF +ATRA therapy ameliorate coagulopathy rapidly in APL patients
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- RIF shows a significant beneficial effect in accelerating the recovery of thrombocytopenia and hypofibrinogenemia for subclinical DIC patients.

Acknowledgements

- All the patients involved in this study
- My colleagues



Thanks for your attention