Thrombohemorrhagic disorders in APL: the unsolved issue

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Background

- ATRA/ATO/CT → significant improvements, but thrombohemorrhagic disorders remain as the unsolved issue:
  - APL is characterized by a life-threatening coagulopathy
  - Hemorrhagic syndromes contribute substantially to morbidity and mortality in APL
  - Thrombosis is a less frequently reported complication (but is also significant)

Outline

- To review the incidence, outcome and prognostic factors
  - Coagulopathy
  - Bleeding
  - Thrombosis
- To discuss the current consensus and controversies on their most appropriate management

Hemorrhagic syndrome in APL: pathogenic mechanism

- Tissue factor release
- Disseminated intravascular coagulation (DIC)
- Fibrinolysis
- Thrombocytopenia
- Fever, exacerbation by chemotherapy?

Incidence of DIC in APL vs AML

- Definition of DIC = thrombocytopenia + both:
  - prolonged prothrombin time and/or activated partial thromboplastin
  - hypofibrinogenemia and/or increased levels of fibrin degradation products or D-dimer
- Hospital La Fe (1978 to 2008; n=1164):

	Fibrinogen <170 mg/dL (%)	DIC (%)
APL	53	68
Non M3 AML	3	10

Incidence of DIC

Patients enrolled in PETHEMA trials

- 1517 patients with available data
- DIC = 59% (+12% induction)
- Hypofibrinogenemia = 46% (+10% induction)
- Median time to resolution = 11 days (range 1-53)

Baseline characteristics in patients with DIC

	No DIC n=631		DIC n=886		P value
	Mean (range)		Mean (range)		
Age, years	44 (2-84)		41 (2-83)		.001
Blasts in PB, %	33 (0-100)		44 (0-100)		<.0001
LDH, UI/L	577 (58-5111)		760 (100-7260)		<.0001
WBC count 10^9/L	8.8 (0.3-460)		14.9 (0.2-188)		<.0001
Triglycerides, mg/dL	163 (22-600)		189 (35-850)		<.0001
GOT, UI/L	37 (5-432)		42 (7-447)		.007
CD34 expression %	12 (0-100)		15 (0-100)		.02
CD2 expression %	15 (0-100)		20 (0-100)		.02

- DIC also also associated to FLT3-ITD (.001), M3v (.03), female gender (<.0001)

Complications according to DIC

	No DIC n=631	DIC n=886	P value
	n (%)	n (%)	
Induction death	51 (8.1)	78 (8.8)	.40
Hemorrhage at presentation	443 (70)	753 (85)	<.0001
CNS bleeding	10 (1.7)	39 (4.6)	.004
Thrombosis at presentation	9 (1.4)	23 (2.6)	.01
CNS thrombosis	0 (0)	17 (2.1)	.05
CNS relapse	4 (0.6)	18 (2.1)	.04

Incidence of fatal bleeding during induction

- Major cause of induction therapy failure in APL patients (5% of hemorrhagic death)
- In contrast with other AML types, in which infection is predominant cause of death

Fatal bleeding in APL before treatment

- The real incidence is unknown

	Total patients (N)	Very early hemorrhagic death (N)	Hemorrhagic death before ATRA start %
PETHEMA LPA96	183	5	**2.7**
PETHEMA LPA99	600	16	**2.7**
PETHEMA LPA2005	873	32	**3.7**
PETHEMA LPA2012	156	6	**3.8**

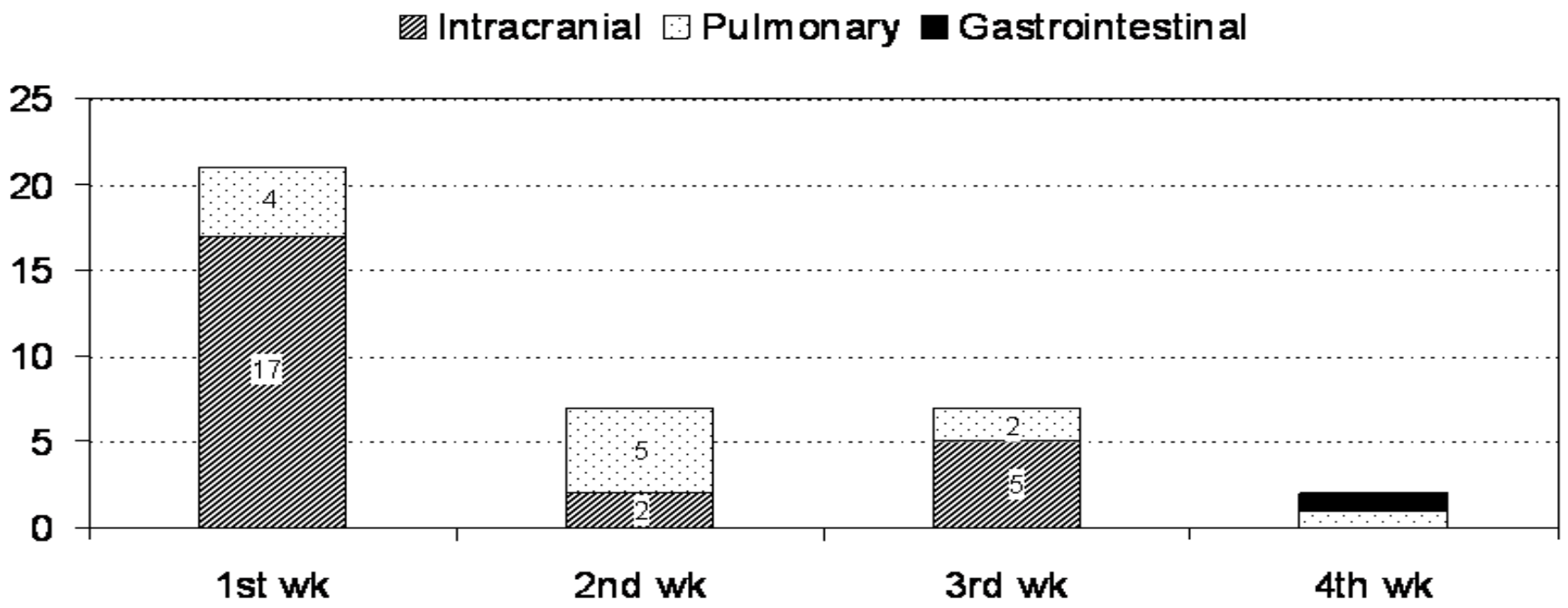
- Swedish registry: 12 out of 105 patients (11.4%) had early hemorrhagic death

PETHEMA LPA99 & LPA2005 Trials
Induction outcome

	LPA99 (n = 562)	LPA2005 (n = 810)	P
CR (%)	512 (91.2)	746 (92.1)	NS
Causes of failure			
Hemorrhage	28 (5.0)	33 (4.1)	NS
Infection	12 (2.1)	15 (1.9)	NS
Differentiation syndrome	8 (1.4)	7 (0.9)	NS
Other	2 (0.4)	8 (1.0)	NS

Time and localization of lethal bleeding

- Almost exclusively due to intracranial (65%) and pulmonary hemorrhages (32%)
- Early onset



De la Serna *et al*. Blood, 2008

Induction Therapy with AIDA Regimen
Prognostic factors of induction death

Bleeding
Creatinine > 1.4 mg/dL
PB blast count ≥ 30 x 10^9/L
Coagulopathy

Infection
Age ≥ 60 yrs
Male gender
Fever

Differentiation syndrome
ECOG ≥ 2
Albumin ≤ 3.5 g/dL

De la Serna *et al*. Blood, 2008

Incidence of life-threatening bleeding after complete remission

- Similar to other AML (thrombocytopenia and other factors influencing)
- 4 out of 28 deaths (14%) during consolidation and maintenance courses in the PETHEMA protocols were due to intracranial hemorrhage

Thrombosis in APL: pathogenic mechanism

- Disseminated intravascular coagulation (DIC)
- Platelet activation
- Release of microparticles / tissue factor
- Exacerbation by ATRA therapy

Thrombosis rate in patients with APL

	Type of study	Patients (N)	Thrombosis at diagnosis %	Thrombosis in induction %
Ziegler et al 2005	Retrospective	49	--	6.1
De Stefano et al 2005	**Prospective**	**31**	**9.6**	**8.4**
Bergamo Study 2006	**Prospective**	**46**	**6.5**	**6.5**
Breccia et al 2007	Retrospective	124	--	5.4
Montesinos et al 2007	Retrospective	760	0.9	4.2
Rodriguez-Veiga et al 2014	**Prospective**	**921**	**4.1**	**9.3**

Risk factors for thrombosis

- Retrospective studies

Risk factors (n=124)	P value
Higher WBC count	0.002
Higher PML/RARa isoform (bcr3)	0.01
FLT3-ITD	0.02
CD2 expression	<0.001
CD15 expression	0.01

Breccia et al. Leukemia (2007) 21, 79-83.

Risk factors (n=740)	P value
Fibrinogen < 170 mg/dl	0.001
M3 variant	0.002
Tranexamic acid prophylaxis	0.049

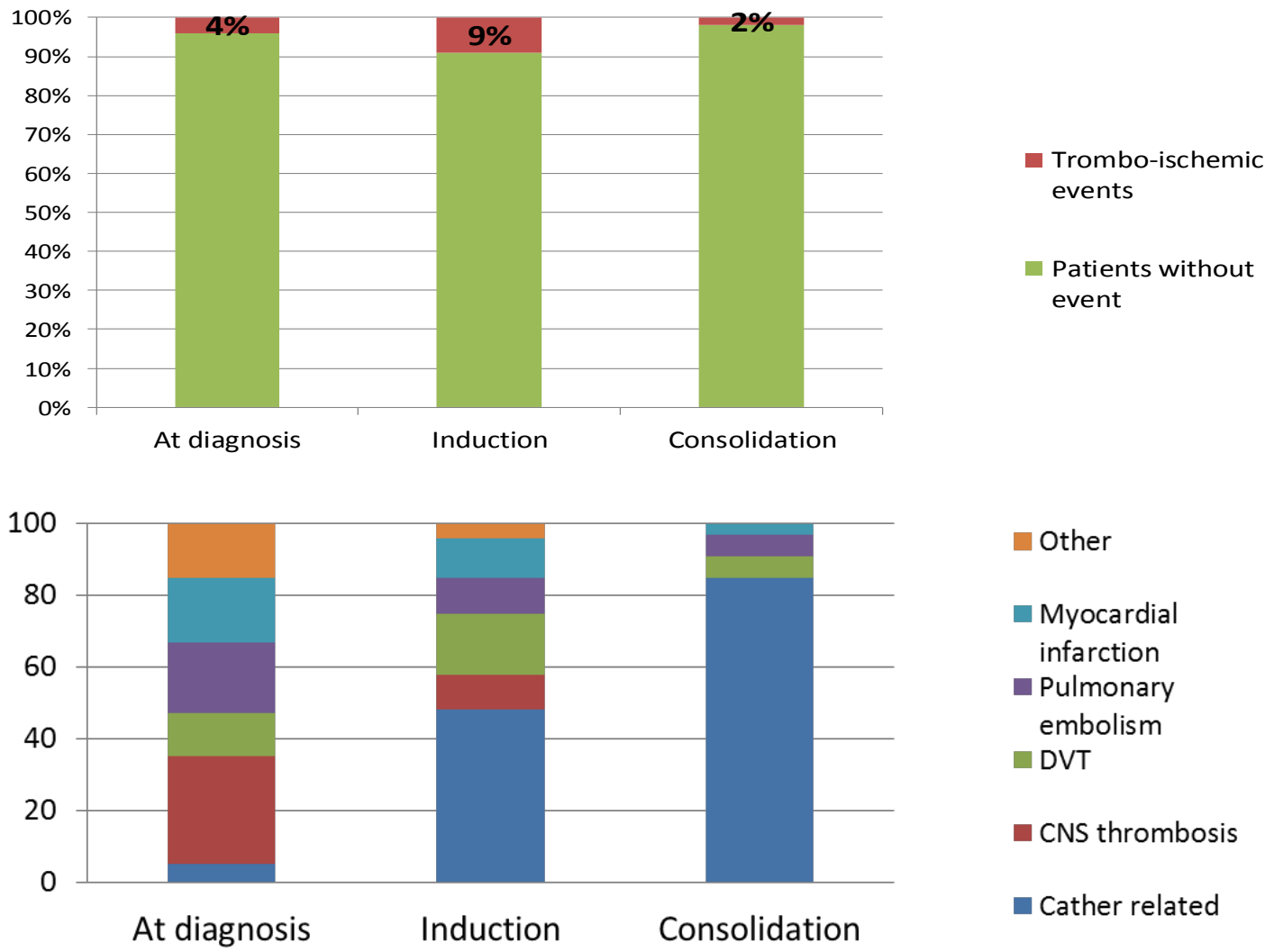
Montesinos P. et al. Blood (ASH anual meeting) 2006

Is differentiation syndrome a risk factor for thrombosis in APL?

	Non-DS (n = 556)	Moderate DS (n = 90)	Severe (n = 93)	*P* value[&]
Outcome and complications of DS				
Death due to hemorrhage no. (%)	22 (4)	5 (6)	10 (11)	0.02
Thrombosis during induction no. (%)	18 (3)	3 (3)	9 (10)	0.008
Platelet units during induction, mean[@]	40.7	44.5	58.9	0.007
Plasma units during induction, mean[@]	4.4	10.1	12.7	< 0.001
Red blood cell units during induction, mean[@]	9.2	10.3	12.3	< 0.001

Montesinos *et al,* Blood 2009

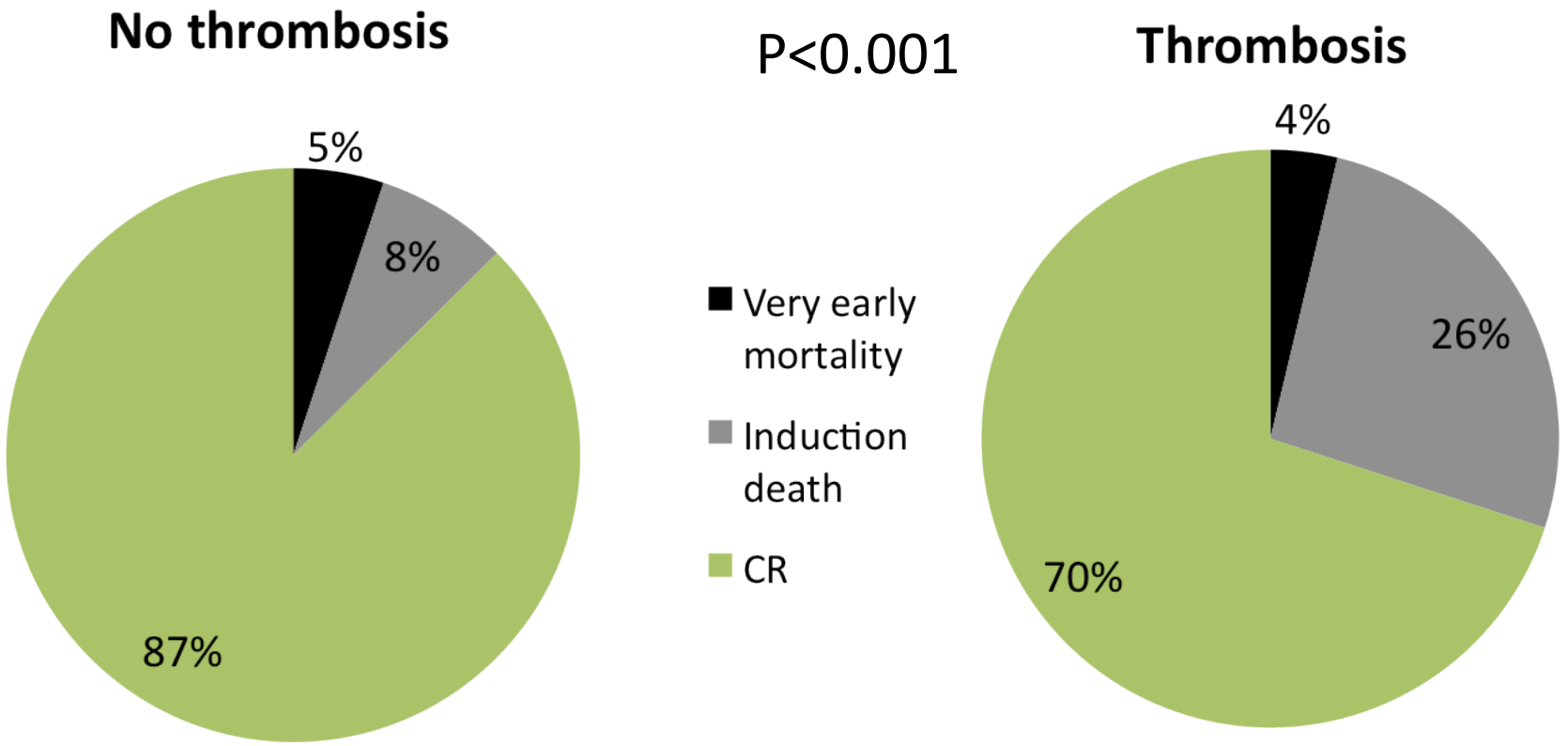
Timing & site of thrombo-ischemic events
PETHEMA Prospective study, n=921



Risk factors for non CVC-related thrombosis
Multivariate analysis

Risk factor	Odds ratio	P value
Higher platelet count	1.01	0.03
Hypoalbuminemia	1.51	0.03
Absence of hemorrhage at diagnosis	2.49	<0.001
Male sex	1.52	0.004
Worse ECOG	1.17	0.04

Is non CVC-related thrombosis related with increased “early” mortality?



Thrombo-ischemic early mortality = 1%

Management of thrombohemorrhagic syndromes

- Start differentiating agents
- Supportive measures to counteract the coagulopathy should be instituted immediately:
  - Fresh frozen plasma and/or cryoprecipitate
  - Fibrinogen concentration and platelet count above 100-150 mg/dL and 30 - 50×10^9/L, respectively

Role of prophylactic heparines

- No benefit for the prevention of early hemorrhagic deaths in a retrospective analysis (GIMEMA group)
- No prospective randomized trials
- Anti-adhesive properties of LMWH could reduce the interaction of APL cells with the endothelium → preventive therapy for the DS?

Role of antifibrinolytic, factor VIIa and prothrombinic complex concentrates

- May enhance the thrombotic risk!
- Use of tranexamic acid no benefit to prevent bleeding
- Anecdotal in patients with APL case reports → rVIIa for life-threatening hemorrhage
- Prothrombinic complex instead of fresh frozen plasma in patients with DIC & fluid overload or DS

Therapy of venous Thrombosis in APL

- No ad hoc studies or guidelines are available
- Bleeding is predominant in APL!! (e.g hemorragic transformation of cerebral stroke)
- However, we should treat thrombosis
  - Remove catheter if applicable
  - Non-fractionated heparines
  - LMWH → adapted to platelet counts

  (70-80% if <70 X 10^9 /L; 50% if <50 X 10^9 /L; stop if <30 X 10^9 /L)

Conclusions

- Hemorrhage is the predominant manifestation of the complex coagulopathy in APL
- Major cause of death before and during induction therapy
- Thrombosis is a probably underestimated life-threatening manifestation
- The knowledge of prognostic factors and pathogenetic mechanisms is crucial
- Scarce date in the clinical setting of chemo-free regimens

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