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Early deaths as the most significant threat to APL patients in real life

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History of ED data from the Swedish Registry

- In late 2000th, we first evaluate APL data from the Swedish Acute Leukemia registry 1997-2006
- Surprising data with an ED rate of approximately 30% in this population-based APL cohort – contrast to clinical trials
- Reported first time here in Rome 2009
- One previous Brazilian study during the ATRA era reported an similar ED rate (Jacomo et al. 2007)
- This has been followed by several other population-based or hospital based reports with ED rates between 10 and 30%.

ED in population-based studies

Study	n	Study years	Age (median)	High risk patients (%)	ED 30 (%)	Death by bleeding (%)
Jacomo 2007	132	2003-2006	36**	36.9	13 (5d) 26 (14d) 32 (ind***)	67
Lehmann 2011	105	1997-2006	54	34	22 (d7) 29 (d30)	41
Park 2011	1400	1992-2007	44		17.3 (1 mo)	
McClellan 2012	70	1997-2009	50	35	19 (7d) 26 (30d)	54
Altman 2013	204	1992-2009	47.5	25	4.9 (7d) 11 (30d)	61
Rahme 2014	399	2006-2011	51	27	9.6 (30d)	31
Paulsen 2014	399	1993-2007 (register-based)			21.8	
	131	1999-2009 (hospital-based)	47.9*	20.6	14.6	
Abrahao 2015	722	1988-2011	0-39*		11(7d) 17 (30d)	
Lehmann 2017	195	1997-2013	56	30	25 (30d)	46

ED in clinical trials in the ATRA era

	n	Study years	Induction treatment	Age (median)	High risk patients (%)	ED30 (%)	Death by bleeding (%)
Di Bona 2000	123	1989-1993	IDA only	38		7.3 (D10) 16,2 (D40)	35
Di Bona 2000	499	1993-1997	AIDA	39		3.8 (D10) 7.6 (D40)	50
Fenaux 1993	101	1991-1992	ATRA alone or CHEMO	40	28	9 v 8	67
Tallman 1997	346	1992-1996	ATRA alone or CHEMO	38	21	11 vs. 14 % (28d)	53
Asou 1998	196	1992-1994	ATRA*	46	26	9	94
Avvisati 1996	20	1993	AIDA	35	25	10	50
Lo Coco 2010	642	1993-2000	AIDA	38	27.6	5.5	37
Lo Coco 2010	453	2000-2006	AIDA	41	28.5	5.6	32
Fenaux 1999	413	1993-1996	ATRA alone or ATRA + CHEMO	46	39 (WBC>5)	7	32
Lengfelder 2000	51	1994-1999	ATRA + CHEMO	43	22	8	75
Schelnk 2004	82	1995-2003	AIDA	43	22	12	71
Sanz 1999	123	1996-1998	AIDA	42		9.8	67
De la Serna 2008	732	1996-2005	AIDA	40	25	9.0	56
Powell 2010	481	1999-2005	ATRA + CHEMO		23	8	
Yanada 2007	279		ATRA**			3	89
Lengfelder 2009	142	1994-2005	ATRA + CHEMO	40	26	7.7	67
Ghavamzadeh 2011	197	1999-2010	ATO	29	19	14.7	90
Illand 2012	124	2004-2009	ATRA + ida + ATO	44	20	3.2	50
Shen 2004	61	2001-2003	ATO vs. ATRA vs. ATRA + ATO	30, 40, 34	23	6.6	100
Ravandi 2008	82	2002-2008	ATRA + ATO + GO for high risk	47	32	8.5	
Lo Coco 2013	162	2007-2010	ATRA + ATO vs. AIDA	44.6 vs 46.6	0	5.2 vs. 0	0
Burnett 2015	235	2009-2013	ATRA + ATO vs. AIDA	47	24	4 vs. 6 5 vs. 9 (60D)	0 with ATO 27 in AIDA

Pre-ATRA studies

Study	n	Study years	Treatment	Age (median)	High risk patients (%)	ED (%)	Death by bleeding (%)
Bernard 1973	80	1963-1971	DNR (after 1969), 6-MP, prednisone, metotraxate metyl GAG			25 (5d) 50 (3 w)	
Drapkin 1977	24	1970-1976	Ara-C, 6-TG, DNR	39	33	54	85
Cordonnier 1985	57	1972-1982	Ara-C and DNR	41*	23 (>15)	12 (5d) 47*	84 (5d) 41*
Kantrajian 1986	60	1973-1984	Ara-C, Amsa, vincristine, prednison, antracyclins	34	30	26*** 43	65 of all EDs
Hoyle 1987	115	1976-1986	DNR, Ara-C, 6-TG	<39		33	84
Sanz 1988	34	1976-1986	DNR	34.5	24	29	60
Rodeghiero 1990	268	1984-1987	DNR, doxorubicin, Ara-C and VP-16	41	31	13 (10d)	74
Cunningham 1990	57	1974-1984	Amsa, Ara-C, 6-TG	<39**	32	21	67
Thomas 1991	67	1974-1989	DNM, Ara-C, vincristine, 6-TG	40	28	30	63
Fenaux 1991	70	1975-1988	DNR alone or DNR+Ara-C	44	21	18	15

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Population-based registries

- To provide valid data, the registry must have a **good coverage** (eg. 95%) of the defined population, **report relevant parameters** with good quality, and have a close to complete **follow-up**
- These studies can give useful results for patient populations that are **not covered by clinical studies**
- **A complement to clinical studies** to guide management of the patients

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Swedish Acute Leukemia Registry

- Since 1958, a **Swedish Cancer Registry, dual report system** were all cancers have to be reported **by law** by pathologists and the treating clinic. Results in very high coverage.

- Since 1997, a Swedish registry with detailed information on AML patients. Continuously matched with the Swedish Cancer Registry (98% coverage).

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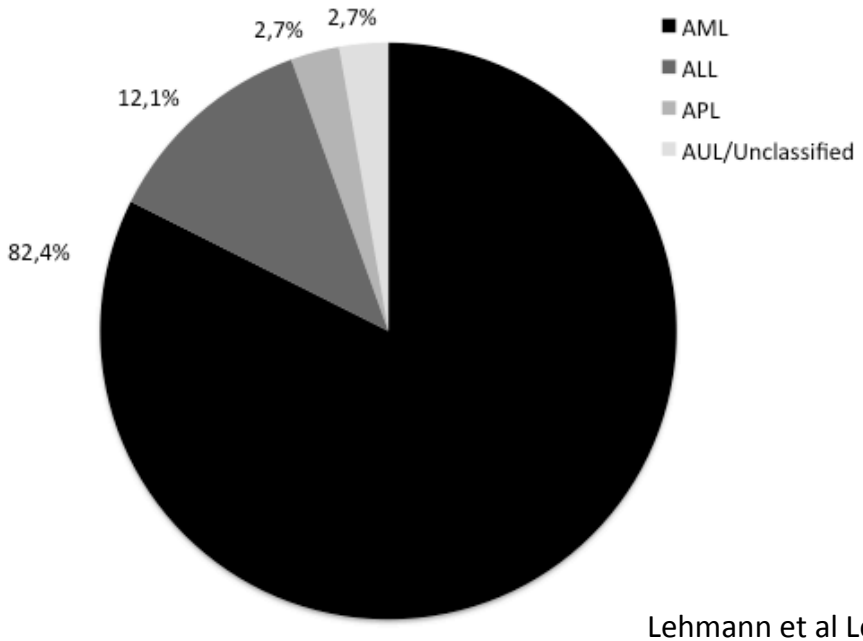

Lehmann et al Leukemia 2011

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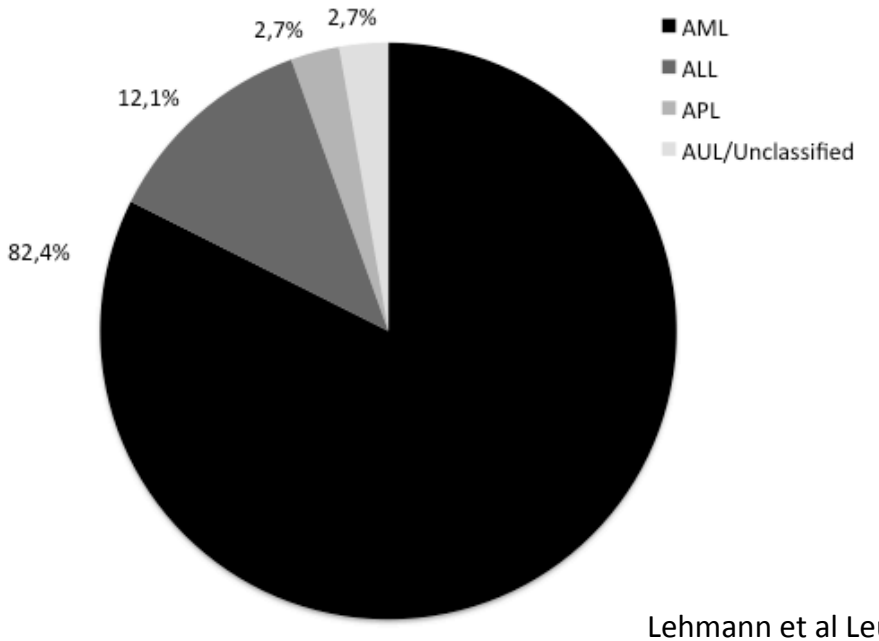

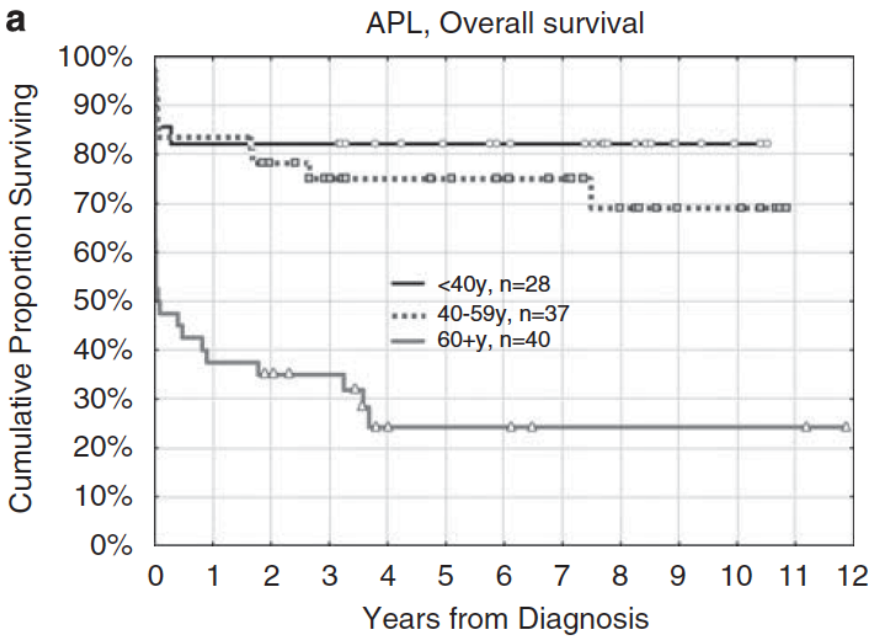

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Follow-up after 2006

- Information to the Swedish hematology community regarding the risk of ED was intensified from 2009

- Guidelines for the early handling of APL patients still the same as before but more forcefully communicated
  - Start ATRA on all AML patients with slightest suspicion of APL (without molecular analysis)
  - Transfusion of platelets to keep platelets > 30-50 x 10^9/L
  - Plasma or fibrinogen concentrates as long as signs of coagulopathy and in order to keep fibrinogen > 1.5 g/L

- We used from 2009 as a study period representing increased awareness

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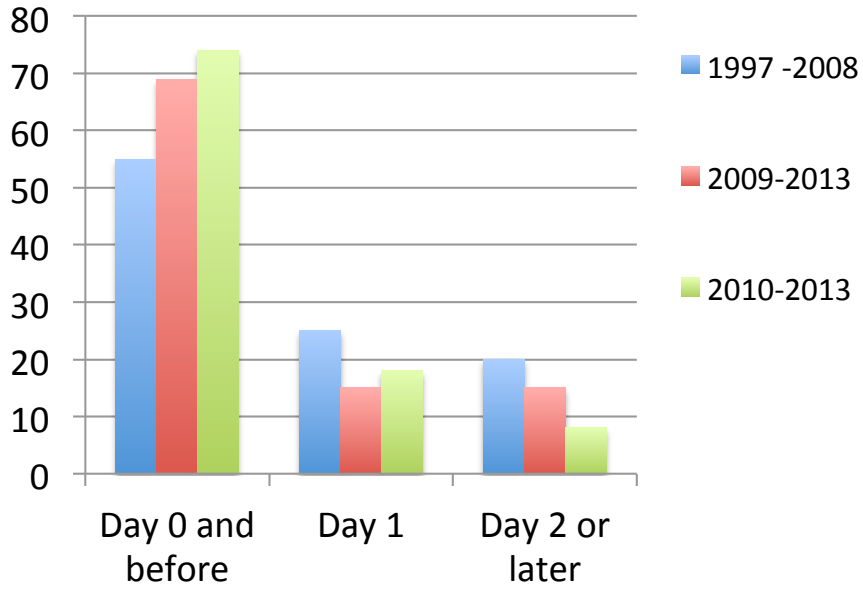

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Follow up on ED study after 2009

	1997-2008	2009-2013	1997-2013
Number of patients	130	65	195
Median age (yrs.)	54	60	56
Mean age (yrs.)	52.4	56.1	53.7
Female (%)	59	46	55
Age >65 (%)	26	37	30
Age >75 (%)	16	10	14
High risk (%)	29	31	30
PS			
0-1	71	70	71
2-4	29	30	29
Early death, all (%)	24	26	25
- high risk* (%)	38	50	44
- low and intermediate risk* (%)	19	15	18

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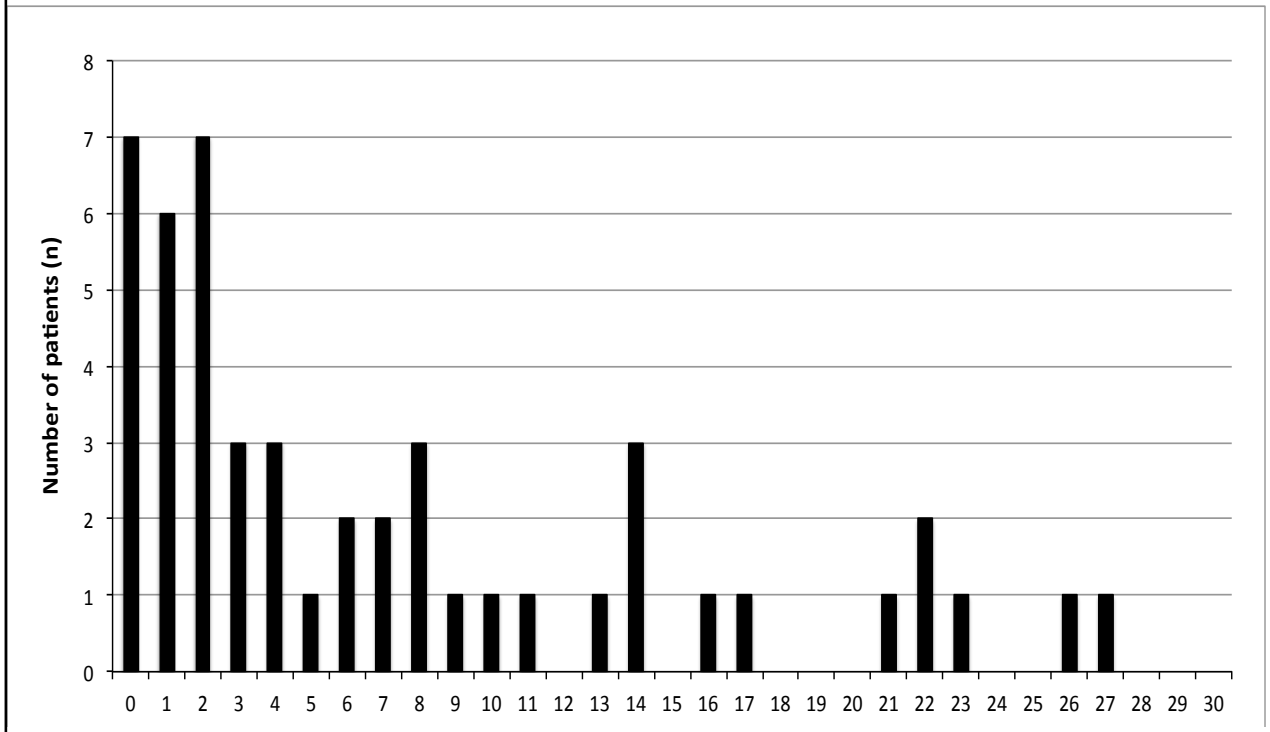
ED results 1997-2013



Days from diagnostic bone marrow examination to ED

Median ED time from diagnostic bone marrow examination: **day 4**

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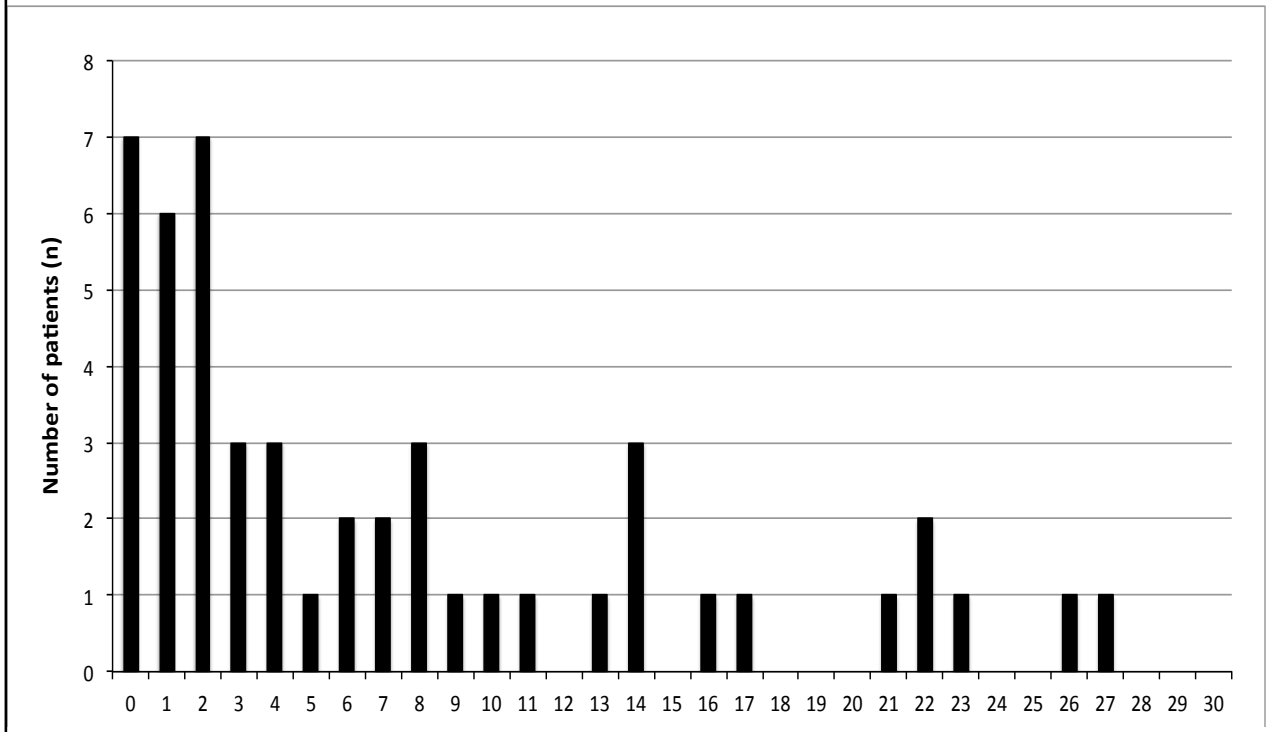

Days from diagnostic bone marrow examination to ED

Age	Percent of APL population
>65	30
>70	20
>75	14

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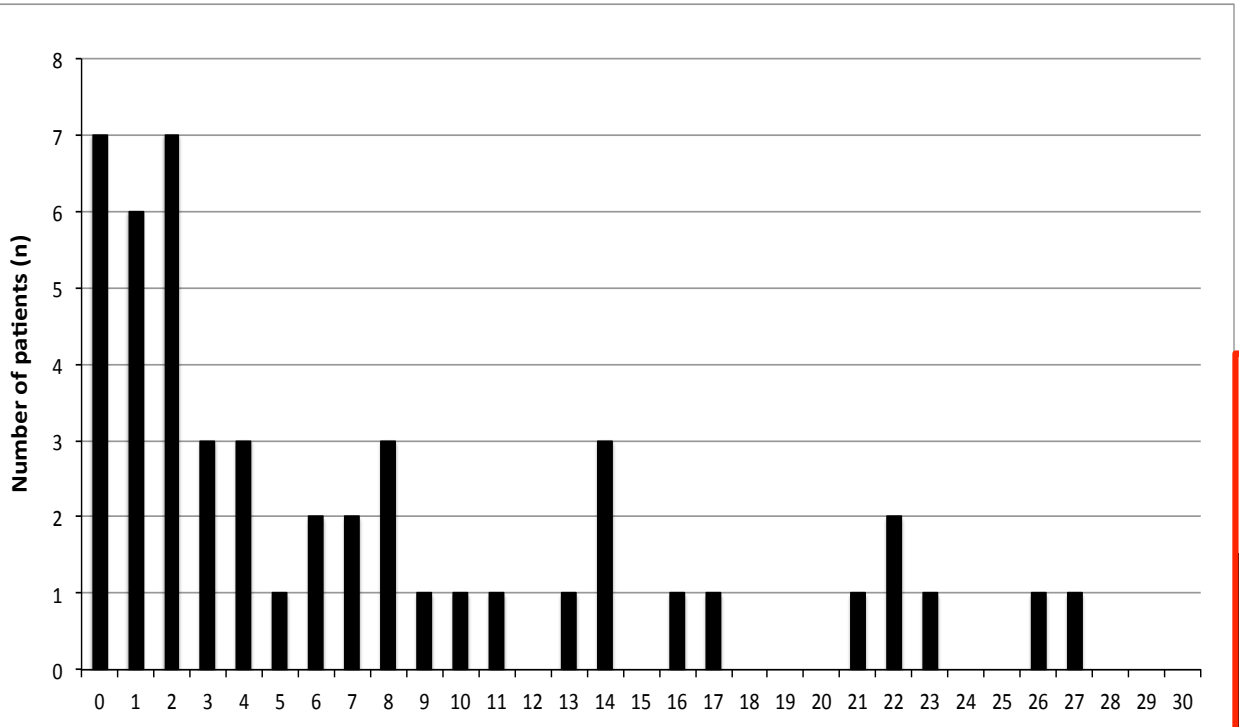

Days from diagnostic bone marrow examination to ED

Age	Percent of APL population
>65	30
>70	20
>75	14

ED – the most significant unmet medical need in APL

Percent ED of all deaths	
Total (1997-2013)	67%
1997-2006	65%
2007-2013	69%
Age <50 years	75%

Median ED time from diagnostic bone marrow examination: **day 4**

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Causes of death

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Cause of death (n=51)	Percent
Hemorrhages	45
Intracerebral hemorrhage	41
Pulmonary bleeding	2
Subdural hemorrhage	2
Sepsis with or without multiorgan failure	14
Respiratory or cardiac failure	14
Multiorgan failure without sepsis	6
Cerebral infarction	4
Myocardial infarction	4
Pulmonary embolism	2
Differentiation syndrome	2
Unknown	10

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Hemorrhages
Dominated by ICH

Median time 4-7 days from diagnosis

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Infections
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Older patients

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Median of 17 days after start of treatment

Maybe underestimated as cause of death

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Hemorrhages
Dominated by ICH

Median time 4-7 days from diagnosis

Infections
Median 21 days after start of treatment

Older patients

Differentiation syndrome
Median of 17 days after start of treatment

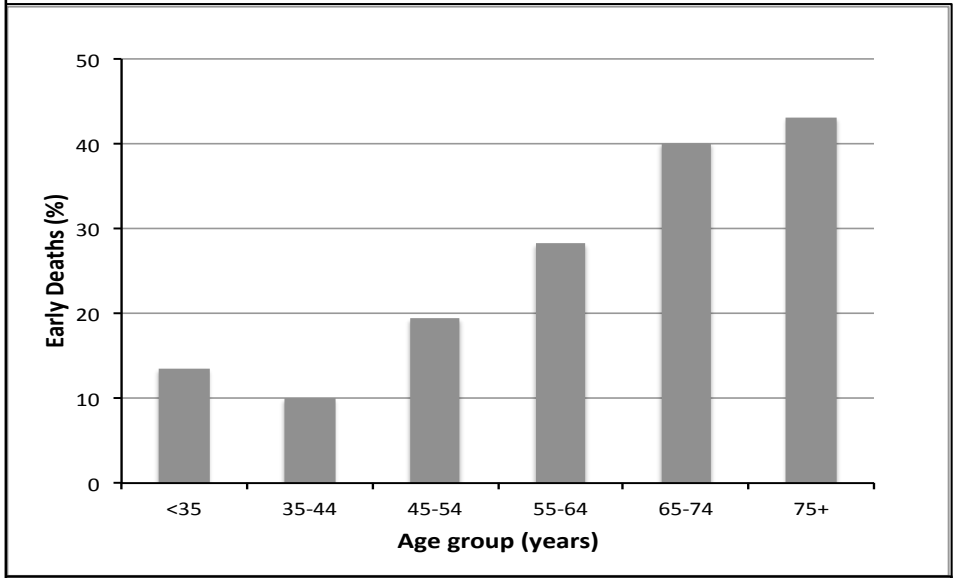
Maybe underestimated as cause of death

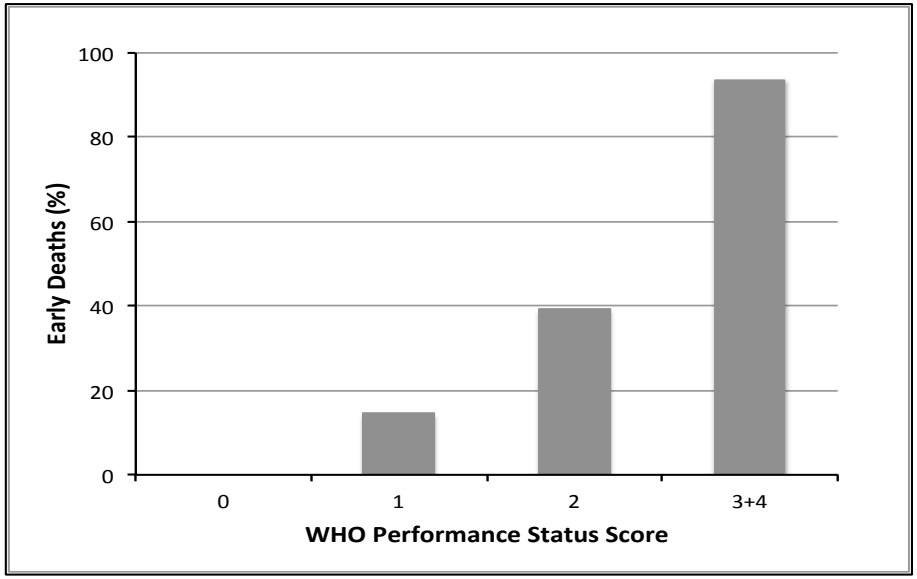
Thrombosis
Important and maybe underestimated

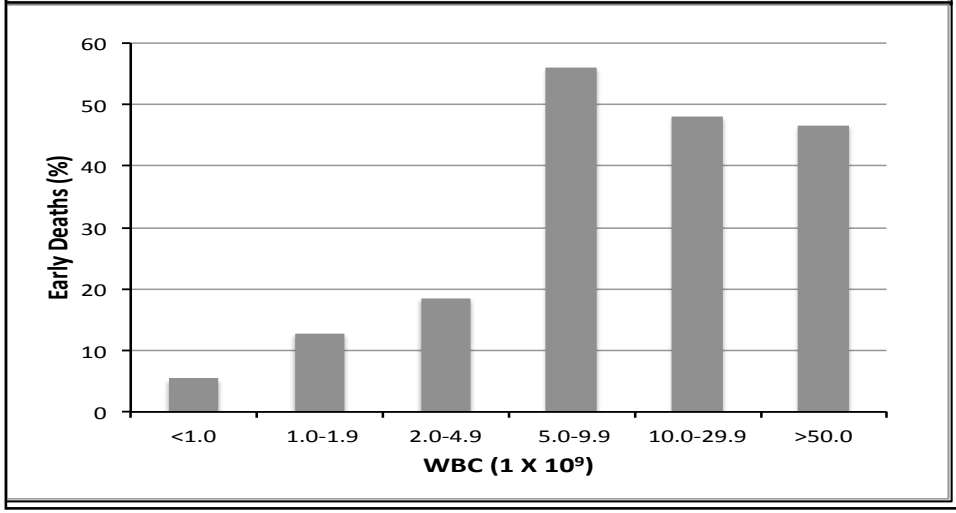
Cerebral thrombosis may also occur together with ICH – may be difficult to distinguish

De la Serna et al 2008, Yanada et al 2007 Breccia et al 2010, Fenaux et al 1999

Risk factors for early death Swedish Registry 1997-2013



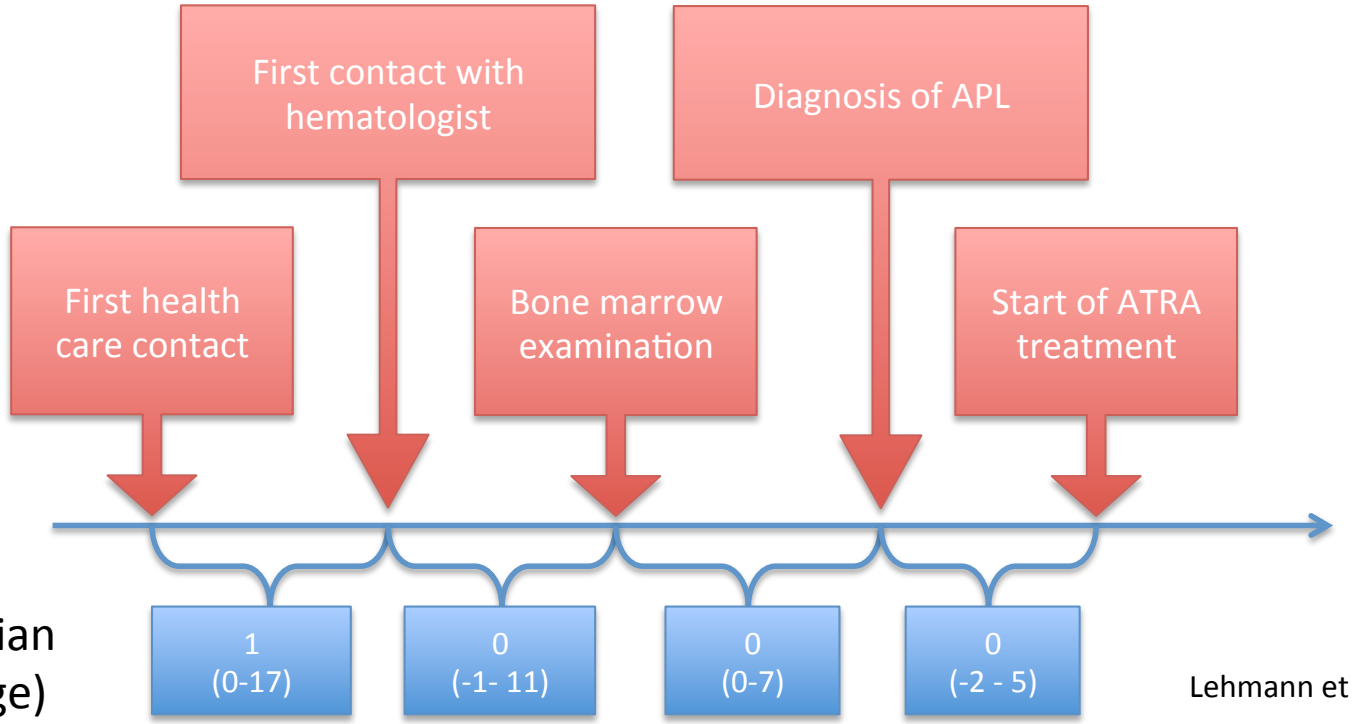




In univariate analysis also platelets and creatinine were risk factors

Lehmann et al Leukemia 2017

Diagnosis and supportive care 1997-2006



Lehmann et al Leukemia 2011

	ED	Non-ED
Threshold. for plt. transfusion (mean and range)	35 (10-50)	33 (10-50)
Received plasma and/or coagulation factor concentrates (%)	Yes 41% No 31% No info. 27%	Yes 49% No 35% No info.16%

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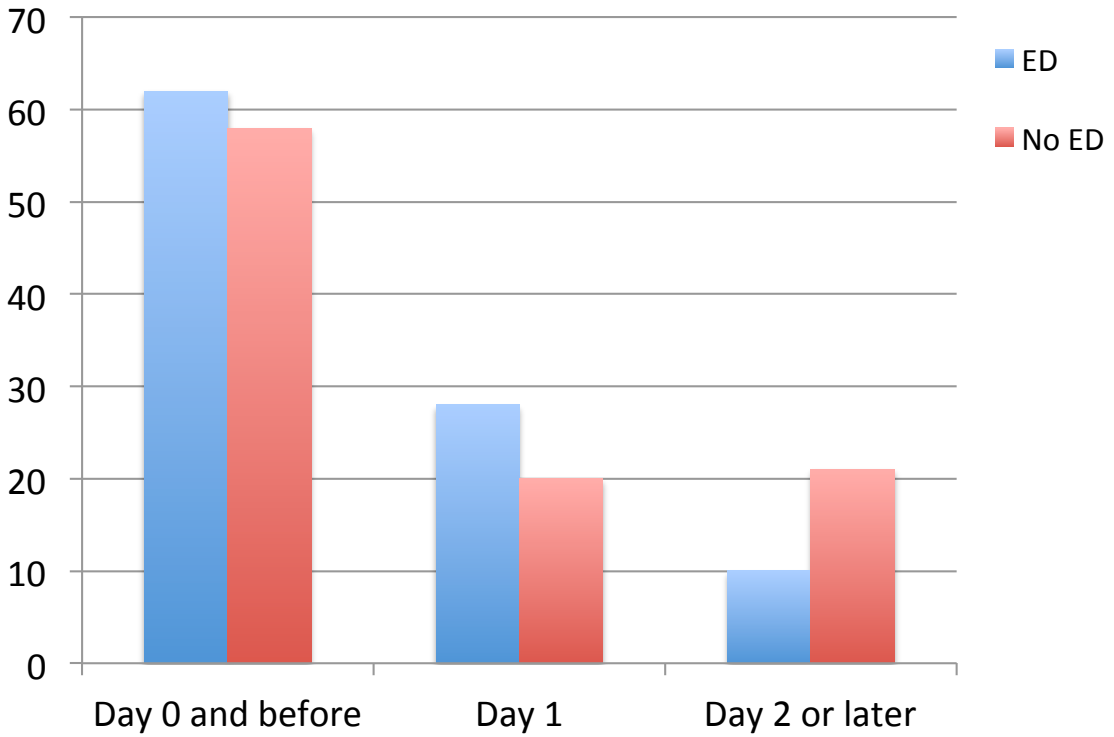
Time to ATRA from BM exam in ED and non-ED patients 1997-2013



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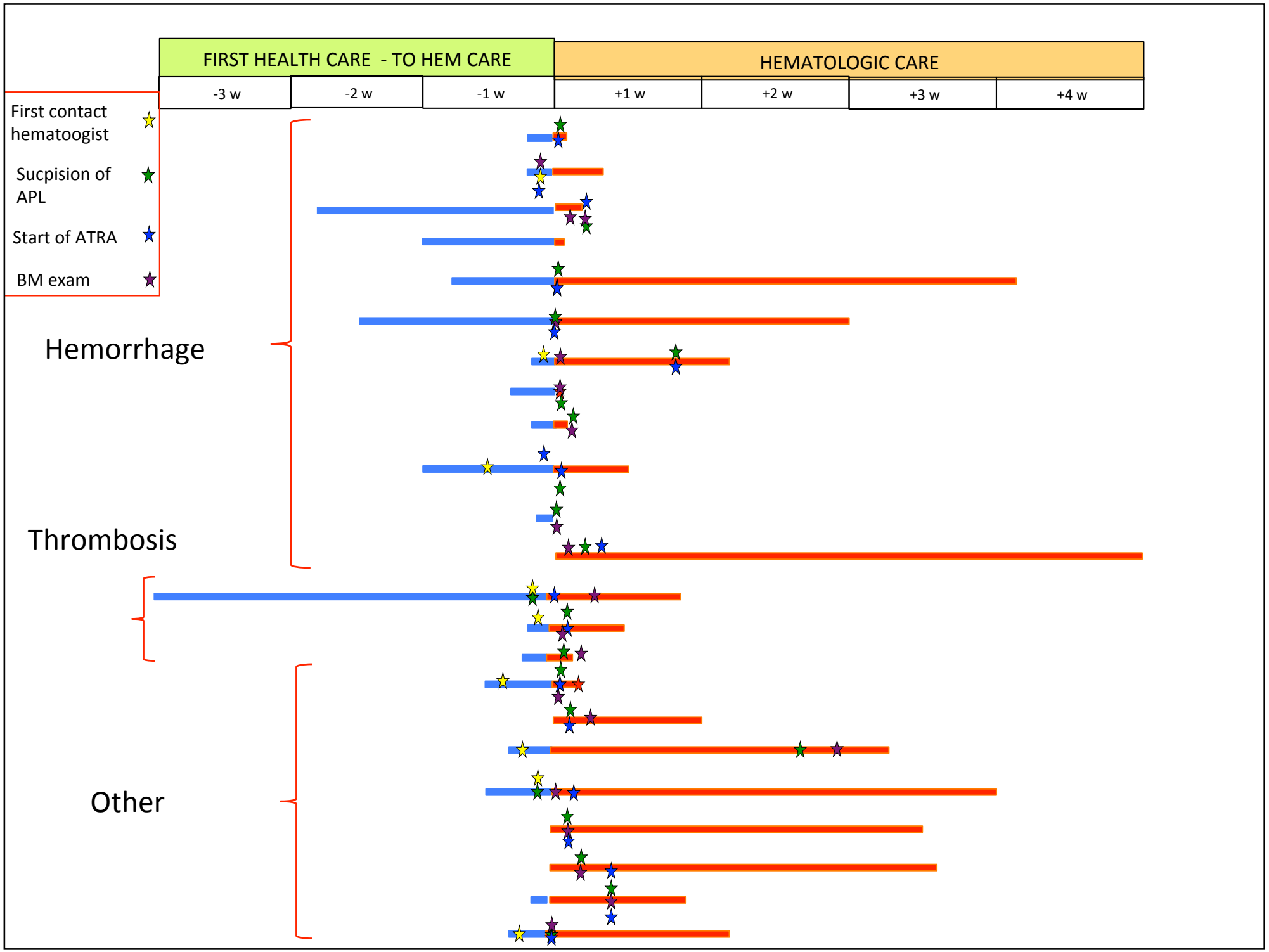
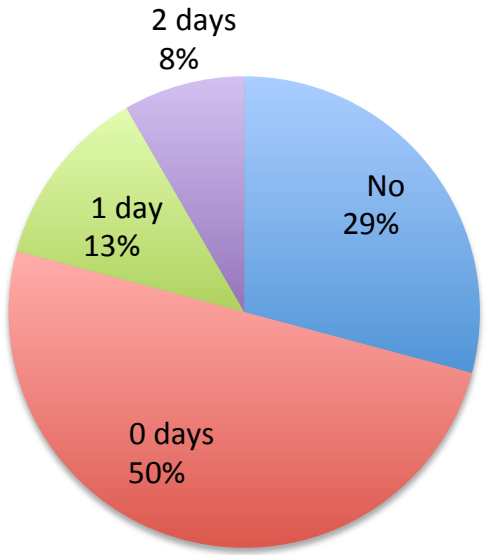
New study of ED 2007 to 2016

- Still high ED despite increase awareness
- How to increase the knowledge about ED and **what are the preventable deaths**
- Study of all ED patients nationwide in Sweden 2007 to 2016
- Identification of patients through the registry
- Not based on registry data but review of medical records
- Details on pre-hematologic and hematologic care including supportive care, tracking each transfusion
- Still ongoing work, we show preliminary data today


FIRST HEALTH CARE - TO HEM CARE
HEMATOLOGIC CARE
-3 w
-2 w
-1 w
+1 w
+2 w
+3 w
+4 w
First contact hematoogist
Sucpision of APL
Start of ATRA
BM exam
Hemorrhage
Thrombosis
Other

Data from the ED study 2007-2016

ATRA treatment – days from APL suspicion



Pre-hematologic care	
Number of pre-hematological delays >3 days	8 (33%)
- Deviation from optimal clinical practice	3
- No obvious deviation from optimal clinical practice	5

Hemorrhages	
Subdural bleeding	1
Intra cerebral hemorrhages	10
Status of ICH before admission	4
Debut of ICH symptoms the first day in hospital	3
Total with ICH before admission or at day 0	7 (29% of all EDs)

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What else can be done?

- Earlier suspicion
- How to decrease “pre-hematological” delays?
- Increased adherence to guidelines – what is the impact?
- Could guidelines to prevent lethal bleeding be more rigorous?
  - ICU care of all high risk patients with more frequent monitoring and more aggressive transfusion policies
- Does arsenic cause less bleeding? – Early oral arsenic?
- We need **more knowledge about the mechanisms of coagulopathy** in APL and effects of different treatments on coagulation

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ATO as first line and ED

- No significant difference in ED rate between ATO + ATRA and CHEMO + ATRA in the randomized trials but still tendencies (5 vs 0% and 4 vs 6 %)(Lo Coco 2013, Burnett 2015). However, low ED rates in general in these trials
- **ED due to infections** and due to chemotherapy side effects will likely decrease
- **The relative proportion of ED** may increase as deaths from relapse and therapy resistance likely will decrease
- Role of **early** ATO? **Oral** ATO?

Acknolwledgements

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Lars Möllgård

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Lovisa Wennström

Petar Antunovic

Bertil Uggla

Kristina Myhr-Eriksson

Anders Wahlin

Students and post-docs

Anna Eriksson

Anna Ravn

Hilda Forsgren

Gustav Holmgren

Regional Cancer Centre

Ann-Sofie Hörstedt, Lund

Swedish physicians reporting to the registry

APL patients