Differentiation syndrome and others

Luca Guarnera, MD

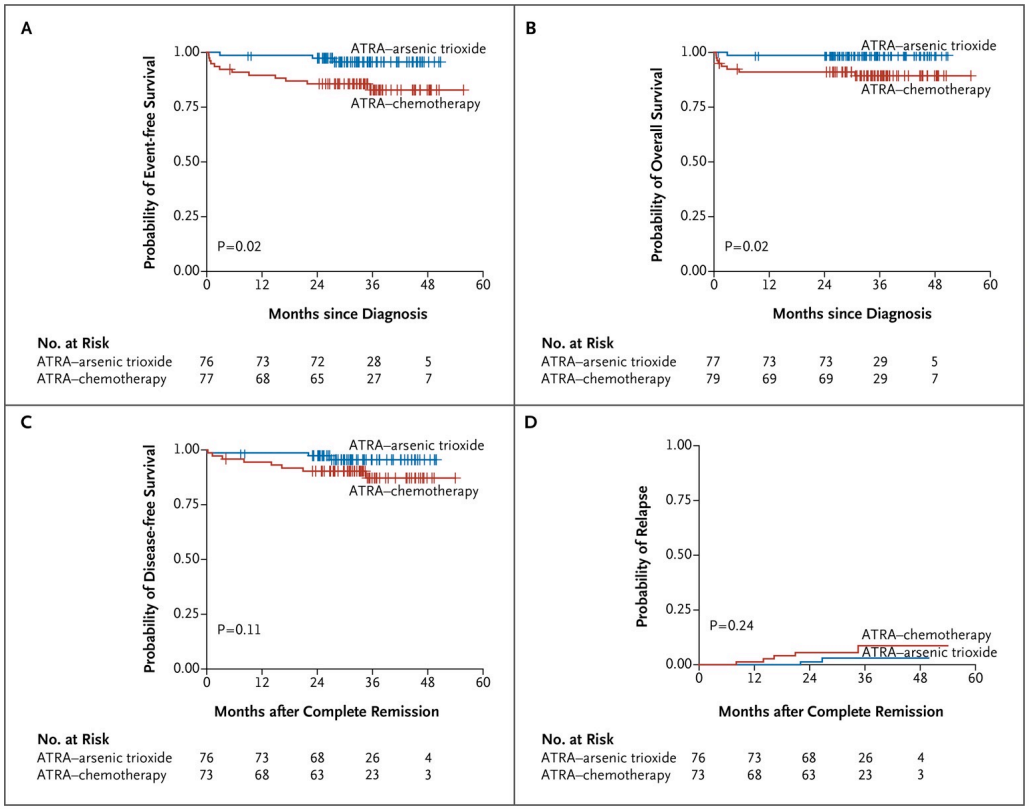
Department of Biomedicine and Prevention, Tor Vergata University, Rome, IT.
Department of Translational Hematology & Oncology Research, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH, USA.

Disclosures of Luca Guarnera

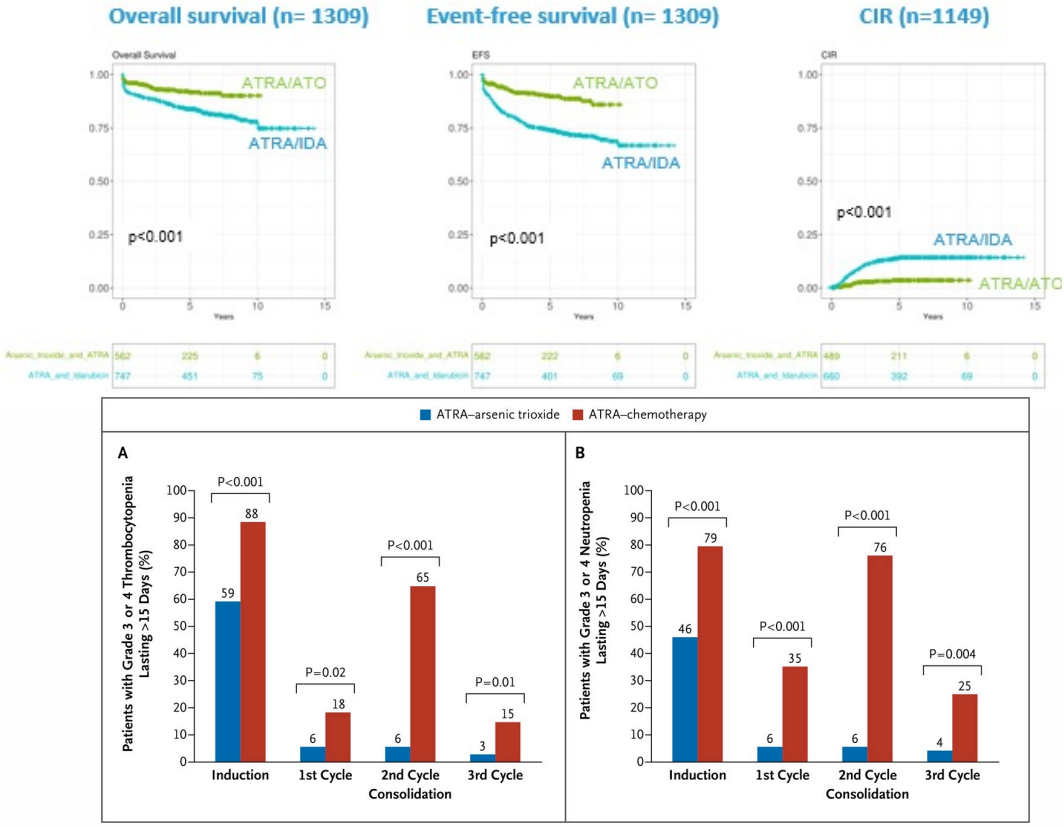
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

Efficacy of ATRA/ATO combination in APL

GIMEMA APL0406 protocol



Harmony APL project

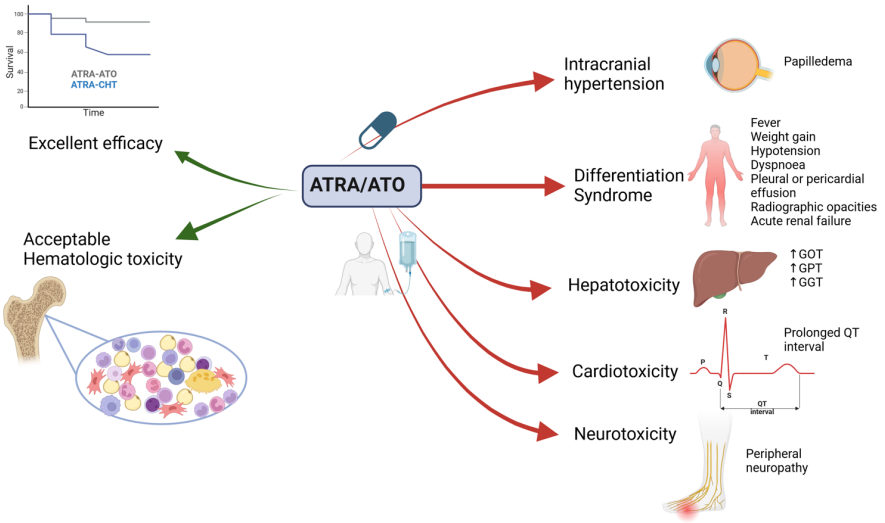


Lo-Coco et al. N Engl J Med. 2013 Jul 11;369(2):111-21.
Guarnera et al. ASH 2023

Outline: Extrahematologic toxicity

- Differentiation Syndrome
- Cardiotoxicity
- Neurotoxicity
- Hepatotoxicity

Incidence
Biology
Management



Toxicity	ATRA-ATO (n=77)	ATRA-CHT (n=79)	P Value
QTc prolongation^	12 (15.6%)	0	<0.001
Hepatic toxicity (grade 3-4)°	43 (63.2%)	4 (5.8%)	<0.001
Gastrointestinal toxicity (grade 3-4)°	3 (4.4%)	7 (9.9%)	0.33
Oral toxicity (grade 3-4)°	0	14 (19.4%)	<0.001

Lo-Coco et al. N Engl J Med. 2013 Jul 11;369(2):111-21.
Guarnera et al. Unpublished

Differentiation Syndrome

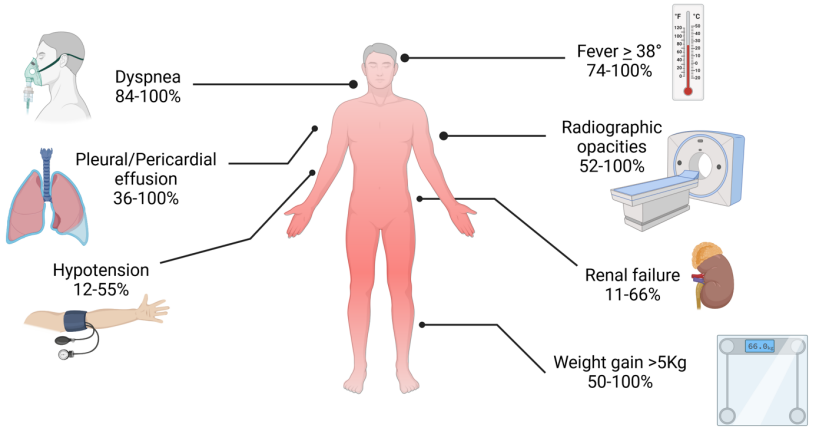
Incidence: 2-50%

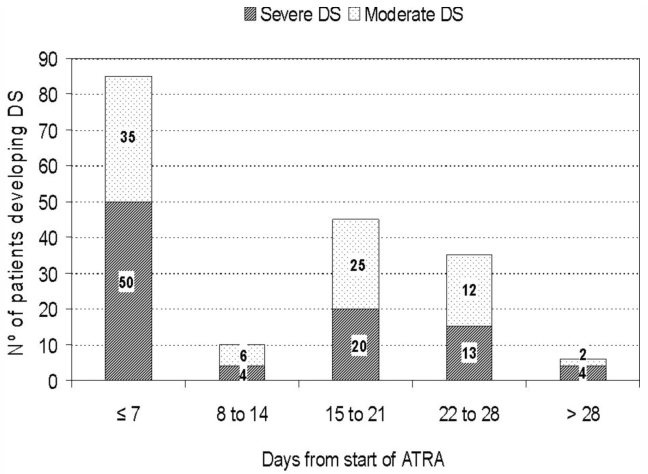
Timing: Median 12 days (Range 0-46)

Manifestations:

- Leucocytosis
- Dyspnea
- Pleural/Pericardial effusion
- Fever ≥ 38
- Radiographic opacities
- Hypotension
- Renal failure
- Weight gain > 5 kg

Diagnostic Criteria





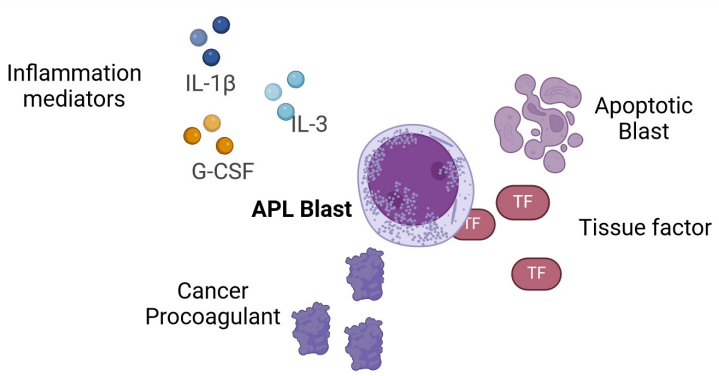
Sthal et al. Br J Haematol. 2019 Oct;187(2):157-162.
Guarnera et al. Front Oncol. 2022 Apr 12;12:871590.
Montesinos et al. Blood. 2009 Jan 22;113(4):775-83.

Guarnera et al. Unpublished
Frankel et al. Ann Intern Med. 1992 Aug 15;117(4):292-6.
Woods et al. Cancers (Basel). 2023 Sep 28;15(19):4767.

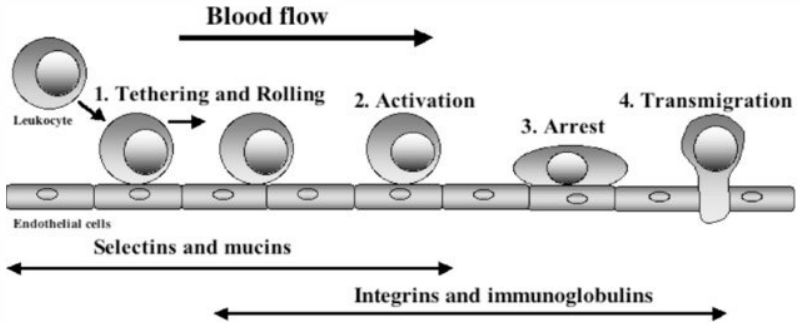
Differentiation Syndrome

Pathogenesis

Cytokine release

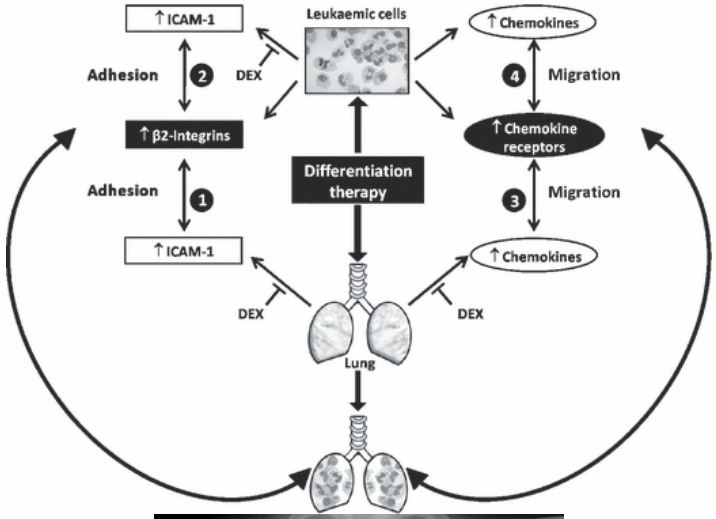


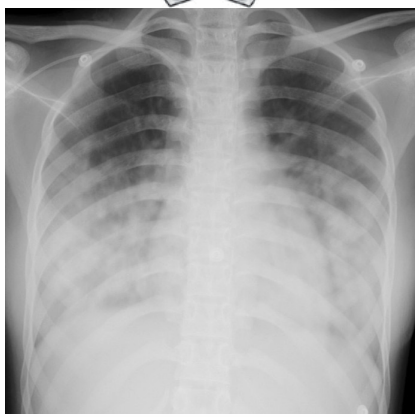
Change in adhesion proteins



Guarnera et al. Unpublished
Rossi et al. Inflamm Allergy Drug Targets. 2008 Jun;7(2):85-93.

Differentiation Syndrome

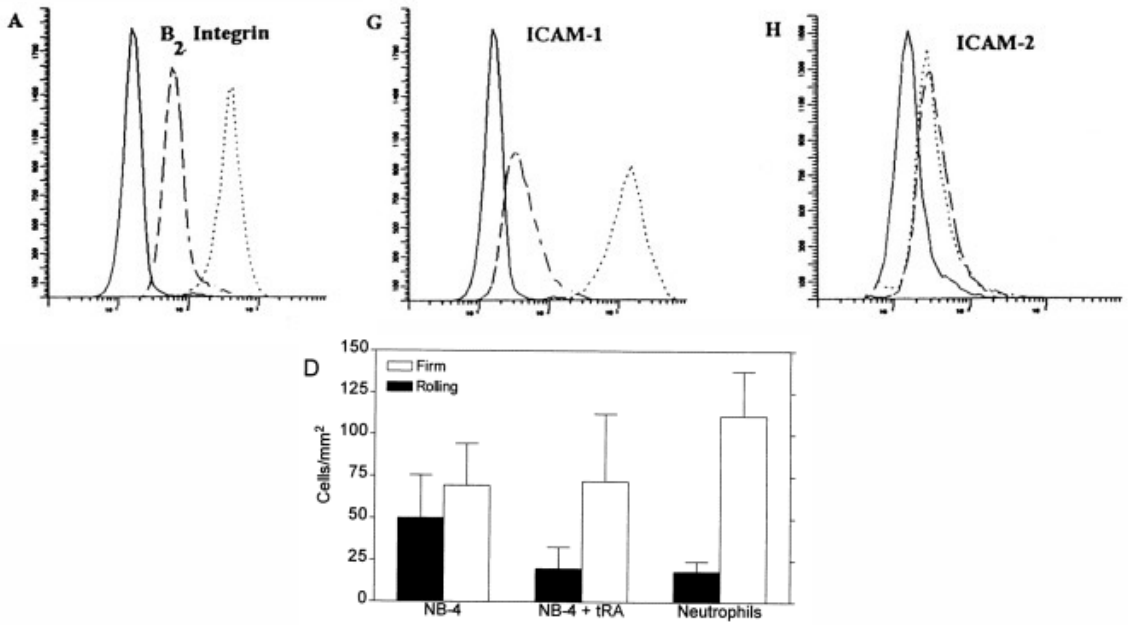




Change in adhesion mechanisms/molecules

↑ **High-avidity β2 Integrins expression**

Surface expression on molecules on NB-4 cells after treatment with ATRA

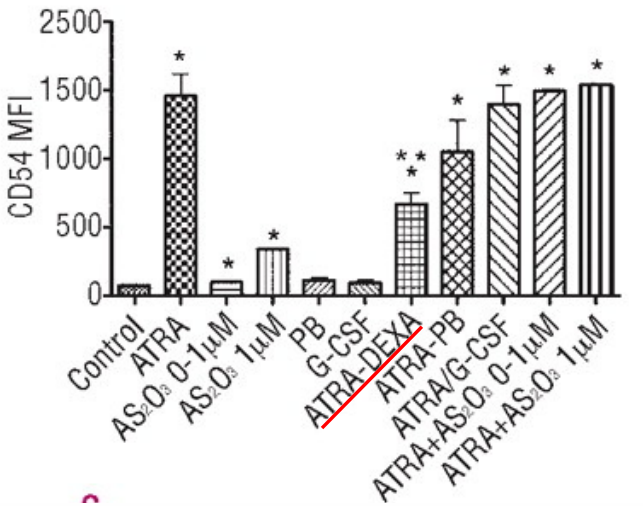


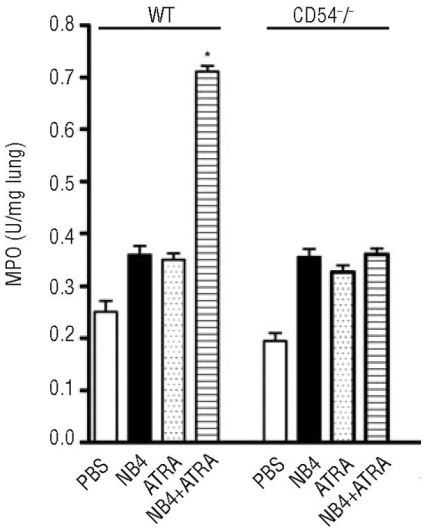
Luesink et al. Br J Haematol. 2010 Nov;151(3):209-20
Sarkar et al. J Med Case Rep. 2021 May 5;15(1):226.
Brown et al. Br J Haematol. 1999 Oct;107(1):86-98.
Larson et al. Blood. 1997 Oct 1;90(7):2747-56.

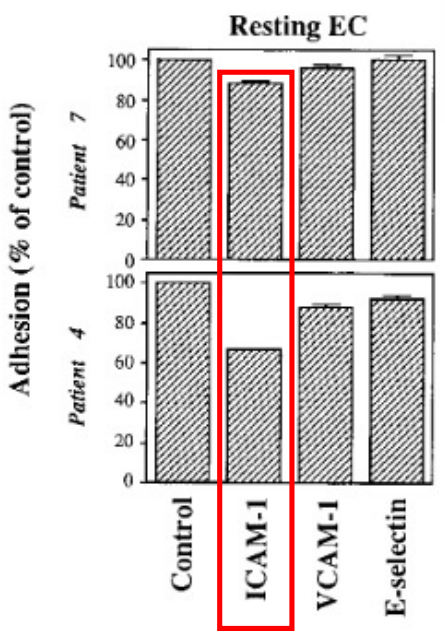
Differentiation Syndrome

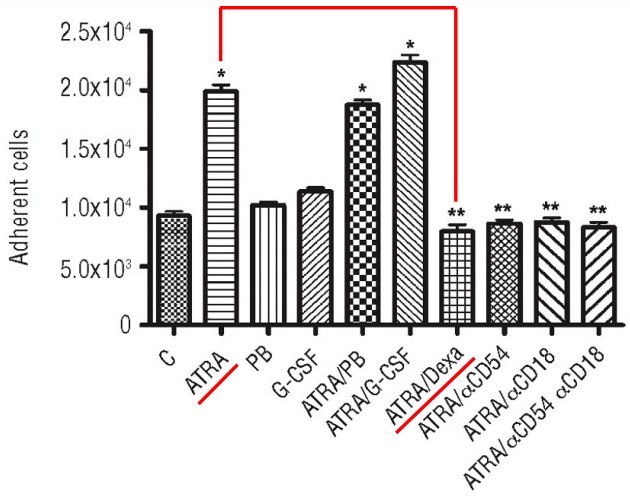
Change in adhesion mechanisms/molecules

↑ ICAM-1 (CD54) expression









Cunha De Santis G et al. Haematologica. 2007 Dec;92(12):1615-22.
Taraboletti et al. Int J Cancer. 1997 Jan 6;70(1):72-7.

Differentiation Syndrome

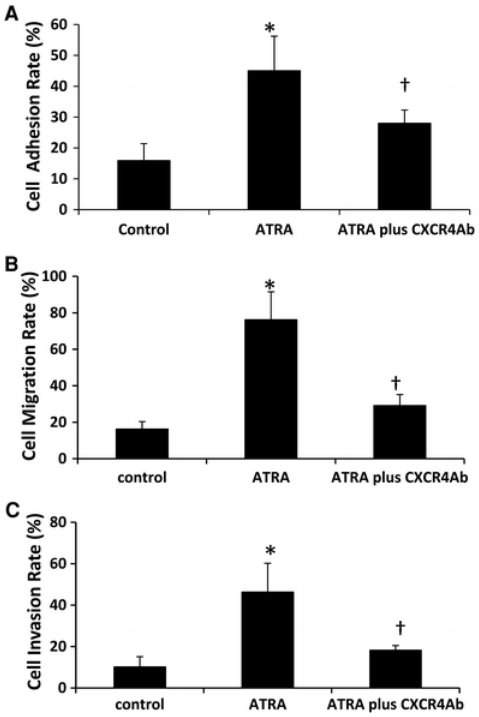
Change in adhesion mechanisms: chemokines

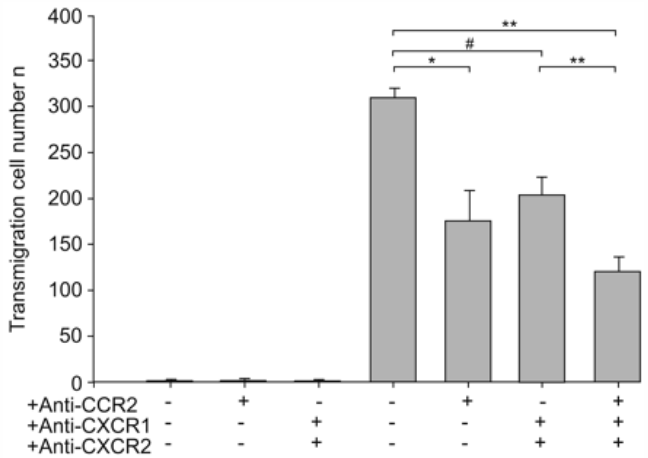
↑ Chemokine receptors expression: CCR1, CCR2, CCR3, CXCR1, CXCR2, CXCR4

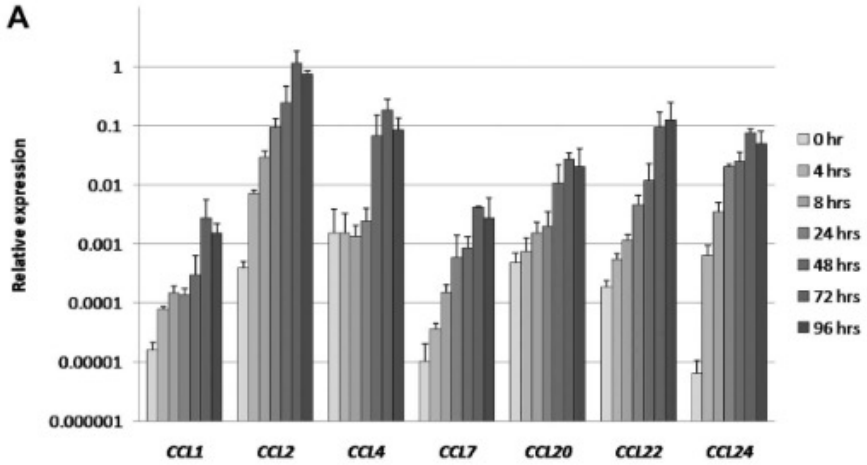
→ Implicated in the pathogenesis of ARDS through interaction with CCL2 and CXCL8

→ Leukemic cells trafficking through interaction with CXCL12

↑ Chemokine production and expression: CCL1, CCL2, CCL4, CCL22



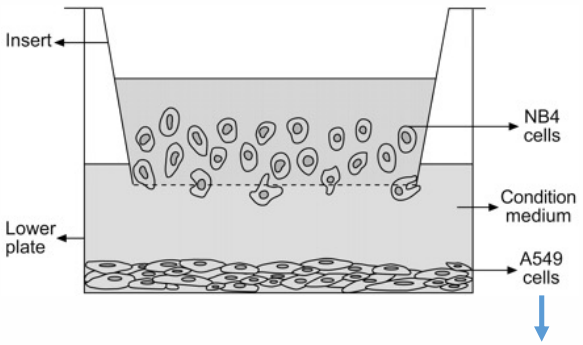




Zhou et al. Int J Hematol. 2010 Mar;91(2):293-302.
Tsai et al. Eur Respir J. 2008 May;31(5):957-62.
Luesnik et al. Blood. 2009 Dec 24;114(27):5512-21.

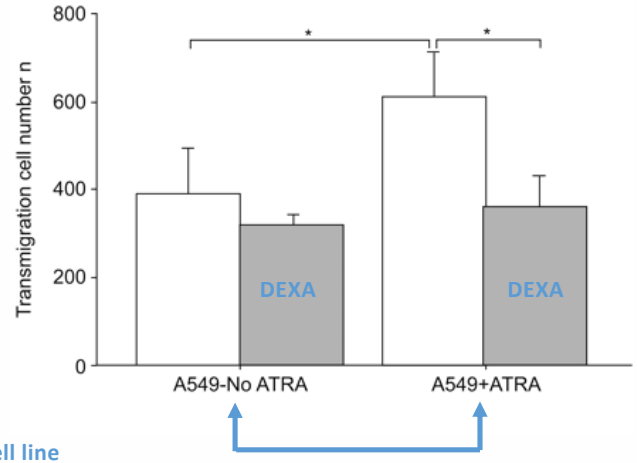
Differentiation Syndrome

Chemokine production in the lungs



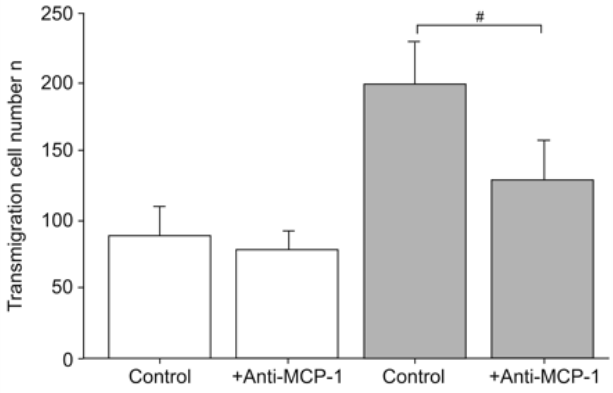
Human alveolar epithelial type II cell line

Change in adhesion mechanisms: chemokines



ATRA-treated NB4 cocultured with

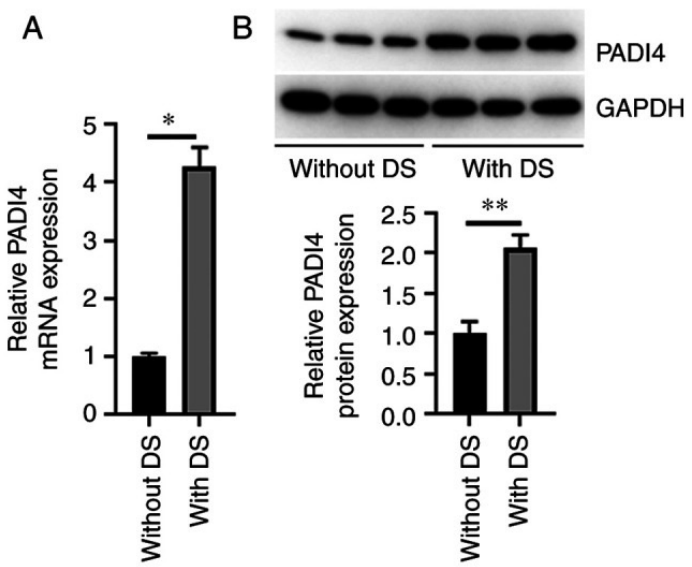
ATRA-treated NB4

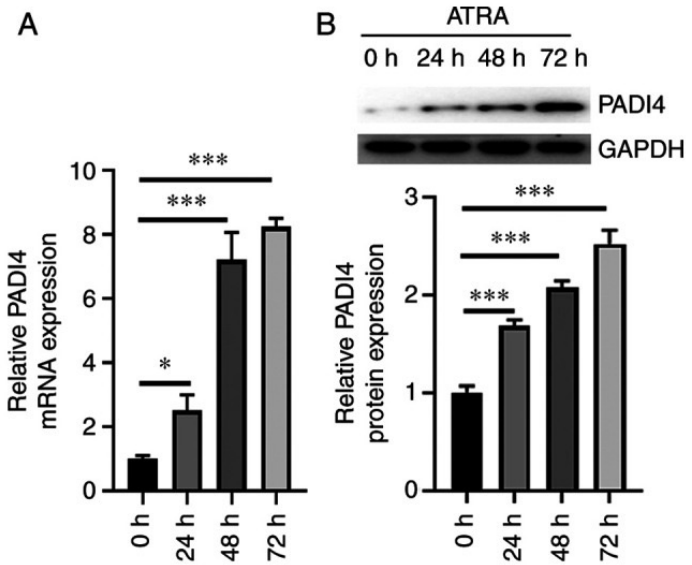


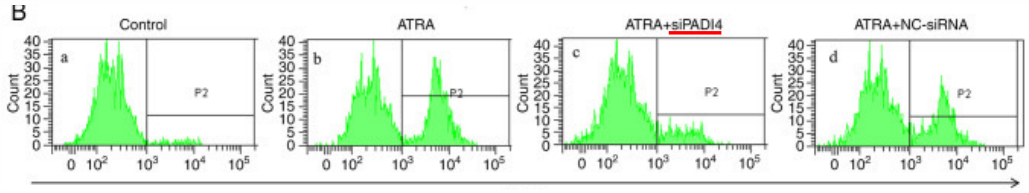
Tsai et al. Eur Respir J. 2008 May;31(5):957-62.
Falconi G. et al, selected presentation, 2024 APL meeting

Differentiation Syndrome

Role of peptidylarginine deiminase 4 (PADI4)







Sun et al. Exp Ther Med. 2023 Jan 31;25(3):118.

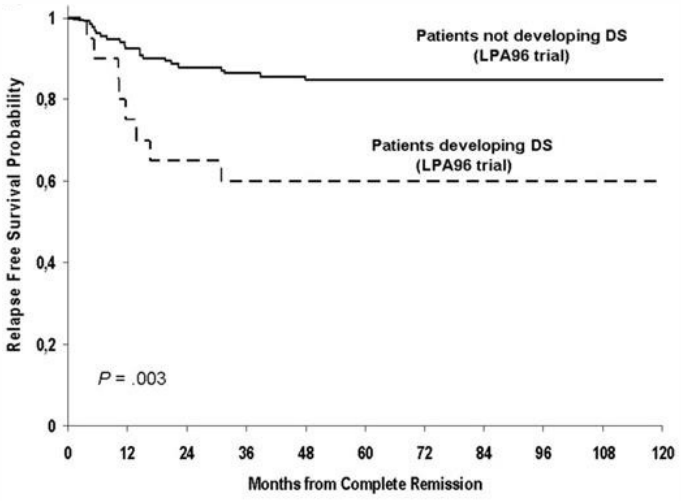
Differentiation Syndrome

Clinical Predictors

High BMI
Hyperleukocytosis
High serum creatinine

Outcome

DS-related mortality ≤1%
Long-term inferior outcome ?



Montesinos et al. Blood. 2009 Jan 22;113(4):775-83.
Breccia et al. Blood. 2012 Jan 5;119(1):49-54.
Jeddi et al. Leuk Res. 2010 Apr;34(4):545-7.
Minamiguchi et al. Ann Hematol. 2020 Dec;99(12):2787-2800.

Prevention & management

Management of hyperleukocytosis (WBC count >10 × 10^9/L) at presentation		
1.10. Cytoreductive chemotherapy should be started without delay, even if the molecular results are still pending:	IV-C	Updated
• For patients to be treated with ATRA + chemotherapy, idarubicin or daunorubicin alone or combined with cytarabine should be given		
• For patients to be treated with ATRA + ATO, cytoreduction can be done with idarubicin (12 mg/m^2) or GO (6-9 mg/m^2)		
1.11. Leukapheresis should be avoided due to risk of precipitating fatal hemorrhage	III-B	Unchanged
1.12. Prophylactic corticosteroids can be given, which may reduce the risk of APL differentiation syndrome	IV-C	Unchanged

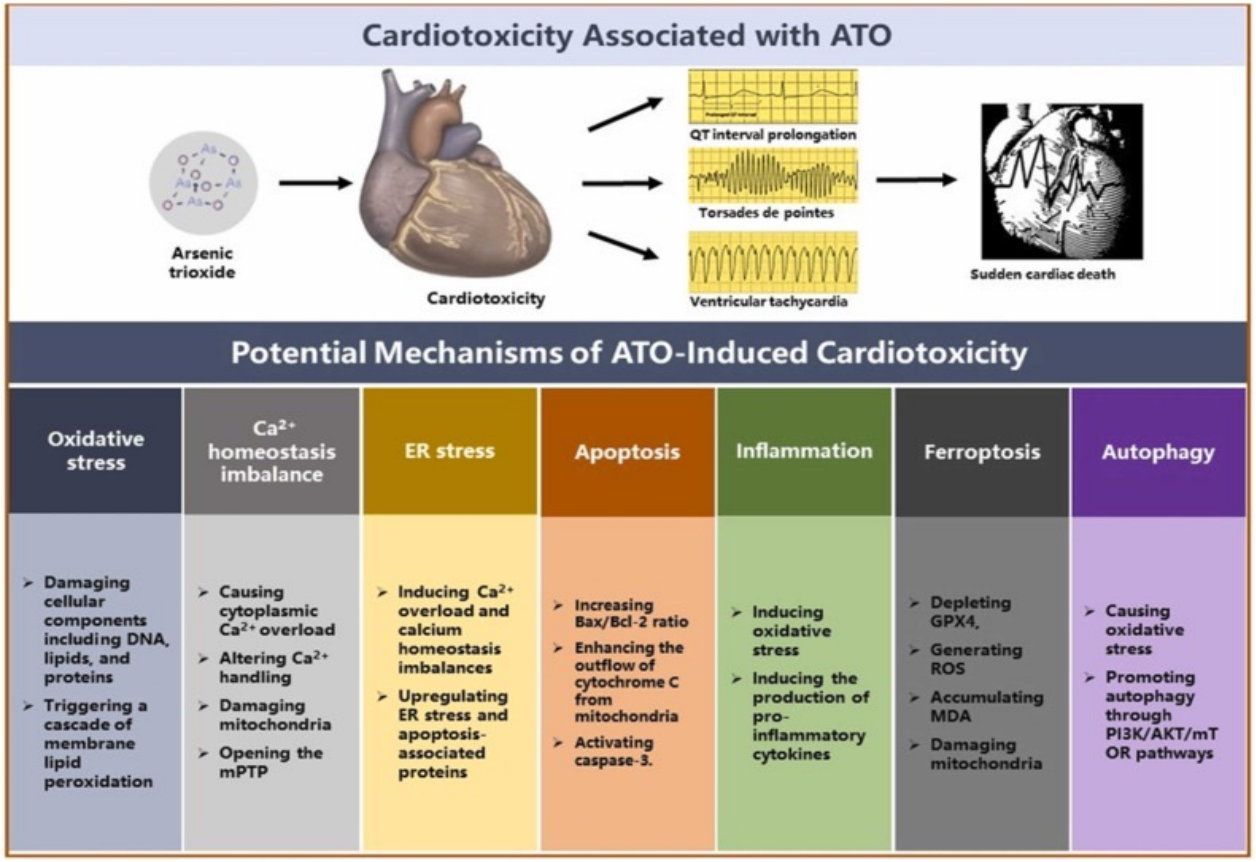
Management of APL differentiation syndrome		
1.13. Corticosteroids (10 mg of dexamethasone IV twice daily) should be started immediately at the earliest clinical suspicion of incipient APL differentiation syndrome; once the syndrome has resolved, steroids can be discontinued and ATO/ATRA recommenced	IIa-B	Unchanged
1.14. Temporary discontinuation of differentiation therapy (ATRA or ATO) is indicated only in case of severe APL differentiation syndrome	IIa-B	Unchanged

Sanz et al. Blood. 2019 Apr 11;133(15):1630-1643.

Cardiotoxicity

Incidence: 10-20%

Manifestations:
- Q-T prolungation
- Torsades de pointes
- Atrial flutter/Fibrillation
- Ventricular tachycardia
- Heart failure



Unnikrishnan et al. Br J Haematol. 2004 Mar;124(5):610-7.
Lo-Coco et al. N Engl J Med. 2013 Jul 11;369(2):111-21.
Burnett et al. Lancet Oncol. 2015 Oct;16(13):1295-305.
Wang et al. Biomed Pharmacother. 2023 Jun;162:114464.

Cardiotoxicity

Management

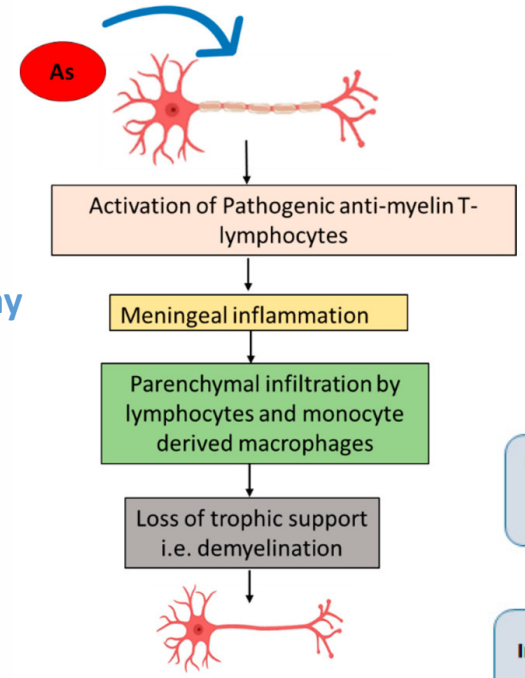
1.18. Treatment with ATO requires careful monitoring to maintain electrolytes in the normal range, keeping the serum potassium above 4.0 mEq/L and serum magnesium above 1.8 mg/dL	IV-C	Unchanged
1.19. Treatment with ATO requires monitoring of the QT/QTc interval at least twice weekly:	IV-C	New recommendation
• For routine ECG surveillance of QT interval prolongation, alternative rate adjustment formulas other than the classical Bazett correction (eg, Fridericia, Hodges, or Sagie/Framingham) should be used		
• Patients with episodes of significant QT prolongation or torsades de pointes, with clinical symptoms, such as dizziness and syncope, or with other risk factors should be closely monitored; telemetered ECG monitoring can be strongly considered in some patients at very high risk		
• If the QT (or QTc for patients with heart rate >60 beats per minute) interval is prolonged longer than 500 ms, ATO should be withheld, the electrolytes repleted (potassium and magnesium), and other medications that may cause prolonged QTc interval sought and possibly discontinued		
• Once the QT/QTc returns to ~460 ms, and the electrolytes are repleted, ATO may be resumed		

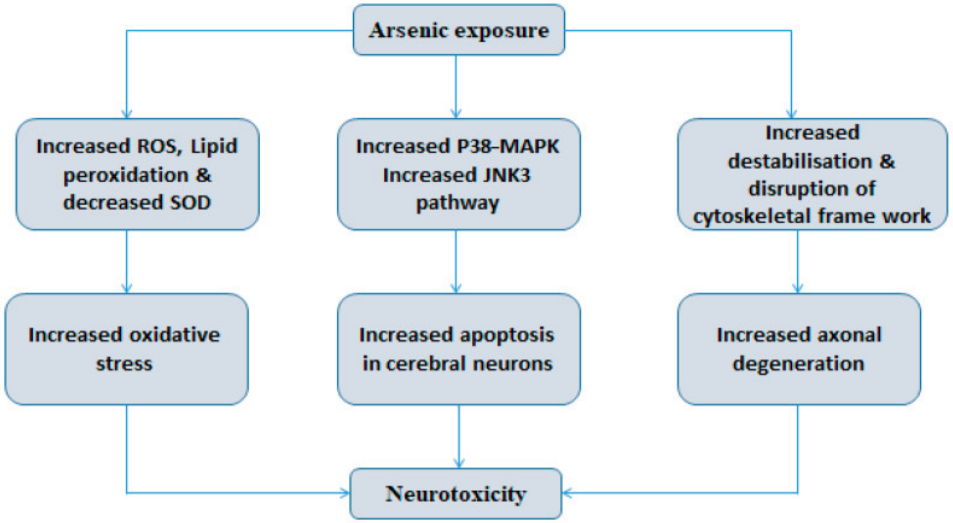
Sanz et al. Blood. 2019 Apr 11;133(15):1630-1643.

Neurotoxicity

Incidence: 5-25%

Manifestations: Peripheral Neuropathy
Encephalopathy
Seizure
Tremor
Ataxia





Thakur et al. Int J Mol Sci. 2021 Sep 17;22(18):10077.
Loh et al. Br J Haematol. 2024 Jan 10.
Lo-Coco et al. N Engl J Med. 2013 Jul 11;369(2):111-21.

Neurotoxicity

	N (%)
Any grade	113/487 (23)
• Grade 1	60 (53)
• Grade 2	37 (32)
• Grade 3	13 (12)
• Grade 4	2 (2)
• Grade 5	1 (1)
Type	
Peripheral neuropathy	104 (91)
• Grade 1	59 (52)
• Grade 2	33 (29)
• Grade 3	10 (10)
• Grade 4	1 (1)
Encephalopathy	3 (3)
Seizure	3 (3)
Tremor	2 (2)
Ataxia	3 (3)
Timing of onset	
Days since start of induction; median (range)	69 (1–623)
Cycle of onset	
• Induction	39 (34)
• Consolidation 1	46 (41)
• Consolidation 2	18 (16)
• Consolidation 3	3 (3)
• Consolidation 4	7 (6)
Cumulative arsenic dose (mg) at onset of neurotoxicity; median (range)	528 (16–1624)
Resolution of neuropathy	
Complete	44 (39)
Residual symptoms	
• Grade 1–2	62 (56)
• Grade 3–4	5 (4)

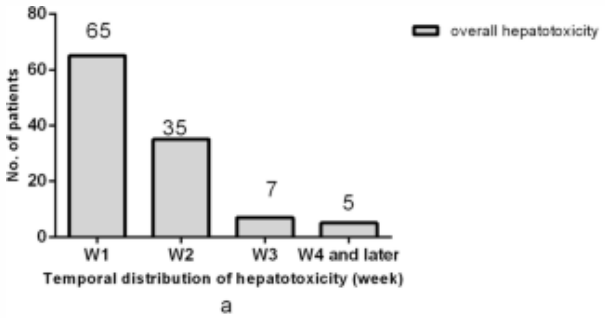
	Univariable analysis			Multivariable analysis		
Covariate	**OR**	**95% CI for OR**	***p* value**	**OR**	**95% CI for OR**	***p* value**
Age	1.01	0.99–1.02	0.311	-	-	-
Male	0.81	0.53–1.24	0.334	-	-	-
BMI						
Non-obese	1	-	-	-	-	-
Obesity class I	1.81	1.04–3.13	**0.036**	1.59	0.86–2.91	0.137
Obesity class II–III	3.93	2.32–6.66	**<0.001**	2.70	1.28–5.72	**0.009**
Weight						
≤100 kg	1	-	-	-	-	-
>100 kg	2.72	1.71–4.34	**<0.001**	0.62	0.23–1.64	0.335
≤120 kg	1	-	-	-	-	-
>120 kg	3.87	1.88–7.95	**<0.001**	-	-	-
<80 kg	1	-	-	-	-	-
80–100 kg	1.38	0.81–2.37	0.233	-	-	-
100–120 kg	2.50	1.37–4.56	**0.003**	-	-	-
>120 kg	5.31	2.44–11.57	**<0.001**	-	-	-
Diabetes	1.02	0.56–1.85	0.949	-	-	-
Pre-existing neuropathy	2.71	1.04–7.05	**0.041**	-	-	-
Liver disease	1.09	0.35–3.37	0.880	-	-	-
CKD stage 3–5	2.27	0.99–5.21	0.053	-	-	-
Chemotherapy-based regimen	0.51	0.32–0.82	**0.005**	-	-	-
Daily arsenic dose						
<10 mg	1	-	-	-	-	-
10–15 mg	1.97	1.12–3.46	**0.018**	-	-	-
>15 mg	5.05	2.67–9.54	**<0.001**	2.04	0.79–5.27	0.141
Cumulative arsenic dose in induction						
<400 mg	1	-	-	-	-	-
400–499 mg	1.29	0.71–2.34	0.403	-	-	-
≥500 mg	3.95	2.22–7.04	**<0.001**	2.18	1.12–4.25	**0.022**

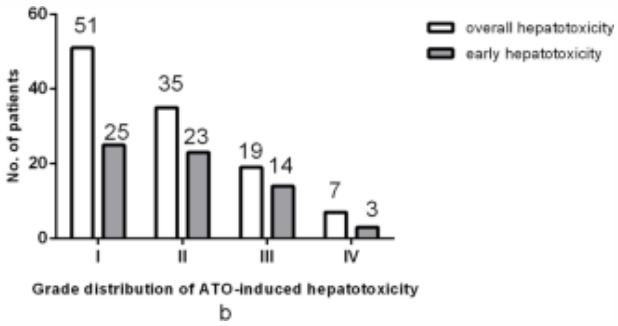
Loh et al. Br J Haematol. 2024 Jan 10.

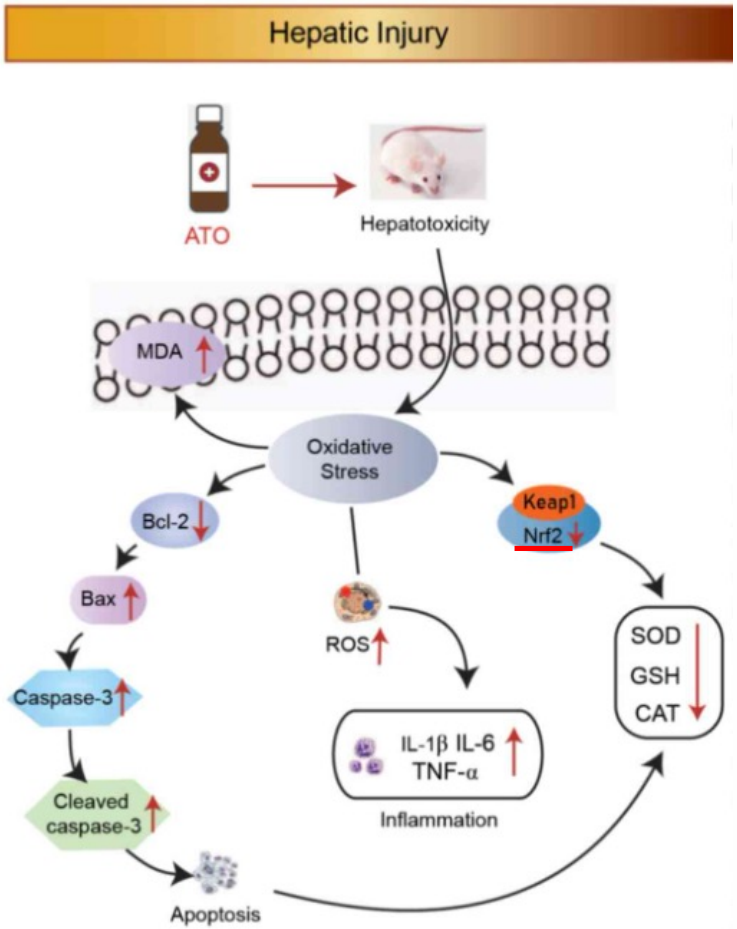
Hepatotoxicity

Incidence: 65-92%

Manifestations: AST/ALT elevation
No clinical symptoms







Liu et al. Mol Med Rep. 2021 Jun;23(6):438.
Zhang et al. Biol Trace Elem Res. 2024 Jan;202(1):122-132.
Lo-Coco et al. N Engl J Med. 2013 Jul 11;369(2):111-21.
Burnett et al. Lancet Oncol. 2015 Oct;16(13):1295-305.

Take home messages

- ATRA/ATO chemofree approach presents a good hematologic and not hematologic safety profile.

- Steroid prophylaxys is effective in preventing differentiation syndrome. Its management, through dexamethasone and temporary ATRA/ATO discontinuation, leads to a safe resolution in almost all cases.

- The administration of ATO requires a careful ECG surveillance and electrolyte monitoring, to promptly recognize cardiotoxicity.

- Neurotoxicity is observed in 5-25% of patients; in most of the cases the manifestations are mild and self-limiting or with mild residual symptoms.

- Hepatotoxicity is frequent, but transient and asymptomatic.

Thanks for the attention!