Myelosupression

World Health Organization
REGIONAL OFFICE FOR Europe

European TB Research Initiative, WHO Regional Office for Europe

6 November 2020

Joint TB, HIV and Viral Hepatitis Programme, Division of Country Health Programmes

Adverse Event of Special Interest

1.Периферическая нейропатия

Myelosuppression

3.Удлинение интервала QTcF

4.Гепатит

5.Неврит зрительного нерва

6.Гипокалиемия

7.Острая почечная недостаточность (ОПН)

Myelosuppression

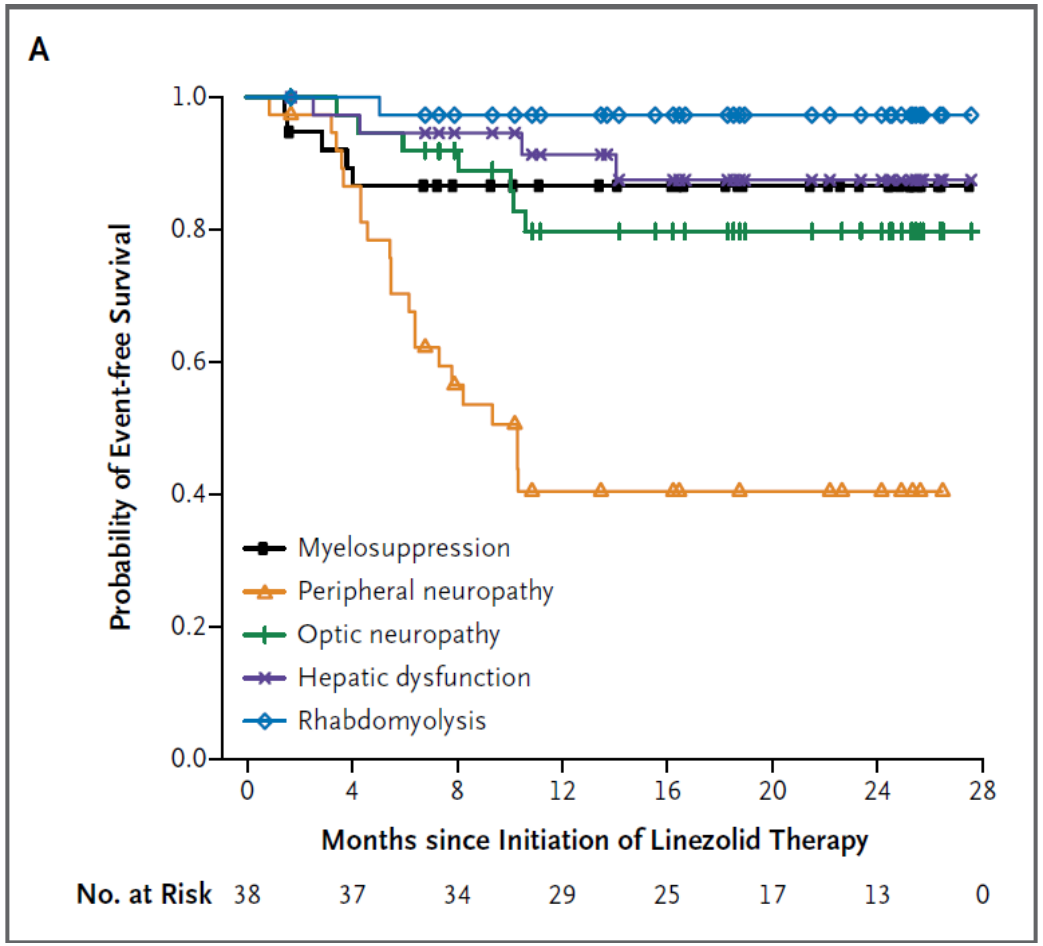
Anemia, thrombocytopenia or neutropenia

Suspected Drug: Lzd

Other possible drugs: AZT, co-trimoxazole

- Mean corpuscular volume (MCV) measurement allows classification of anemia as normocytic, microcytic, or macrocytic. Macrocytic anemia is most likely caused by AZT, but AZT can also cause normocytic anemia.
- If a patient has thrombocytopenia or neutropenia, the most likely cause is linezolid. AZT can cause this reaction, but less often.
- Blood loss (occult gastrointestinal bleeding as a result of peptic ulcer disease) can cause anemia.
- Other causes of anemia (TB, iron deficiency, etc.) are possible, but they are unlikely to occur in the middle of treatment, especially with improvement of patient's clinical condition .

Linezolid for Treatment of Chronic Extensively Drug-Resistant Tuberculosis



n engl j med 367;16 nejm.org october 18, 2012

At Baseline

HIV+ RR-TB Patient

	WBC Leikocīti	6.03 10^9/L	(4.00-9.00)
	NEU% Neitrofīlie	71.4 %	(48.0-78.0)
	NEU# Neitrofīlie (abs.sk.)	4.31 10^9/L	(2.50-7.50)
<<	LYM% Limfocīti	10.3 %	(19.0-37.0)
<<	LYM# Limfocīti (abs.sk)	0.62 10^9/L	(1.00-3.50)
>>	MONO% Monocīti	15.1 %	(3.00-11.00)
>	MONO# Monocīti(abs.sk.)	0.91 10^9/L	(0.200-0.800)
	EOS% Eozinofīlie	2.2 %	(0.50-5.00)
	EO# Eozinofīlie (abs.sk.)	0.13 10^9/L	(0.000-0.400)
	BASO% Bazofīlie	0.5 %	(0.00-1.00)
	BASO# Bazofīlie (abs.sk.)	0.03 10^9/L	(0.000-0.100)
	.		
<	RBC Eritrocīti	3.81 10^12/L	(4.20-5.80)
<	HGB Hemoglobīns	11.10 g/dL	(14.00-16.00)
<	HCT Hematokrīts	34.4 %	(39.0-50.0)
	MCV Vidējais eritrocīta tilpums	90.3 fL	(80.00-97.00)
	MCH Hb vidēja saturs eritrocītā	29.10 pg	(27.00-31.00)
	MCHC Hb vidēja konc. vienā eritroc.	32.30 g/dL	(31.80-36.00)
	RDW-SD RBC sadalījuma plašums-SD	43.3 fL	(37.0-54.0)
	RDW-CV RBC sadalījuma plašums-CV	13.1 %	(11-16)
	.		
	PLT Trombocītu skaits	253 10^9/L	(150-400)
	MPV Vidējais trombocīta tilpums	10.1 fL	(7-12)
	PDW Trombocītu sadalījuma plašums	10.1 fL	(9-17)
	PCT Trombokrīts	0.26 %	(0.17-0.35)
	P-LCR Trombocītu-lielo šūnu attiec.	24.1 %	(13-43)
	.		
	NRBC% Kodolsaturošie RBC	0.0 /100WBC	
	NRBC# Kodolsaturošo RBC (abs.sk.)	0.00 10^9/L	
	.		
	IG% Nenobriedušie granulocīti	0.5 %	(0.00-0.70)
	IG# Nenobriedušie granulocīti	0.03 10^9/L	(0.00-0.07)

RR-TB Patient Post Lung Cancer Surgery and Chemotherapy

	SYSMEX XN1500		
	WBC Leikocīti	6.64 10^9/L	(4.00-9.00)
	NEU% Neitrofīlie	72.0 %	(48.0-78.0)
	NEU# Neitrofīlie (abs.sk.)	4.79 10^9/L	(2.50-7.50)
<	LYM% Limfocīti	16.9 %	(19.0-37.0)
	LYM# Limfocīti (abs.sk)	1.12 10^9/L	(1.00-3.50)
	MONO% Monocīti	8.9 %	(3.00-11.00)
	MONO# Monocīti(abs.sk.)	0.59 10^9/L	(0.200-0.800)
	EOS% Eozinofīlie	0.5 %	(0.50-5.00)
	EO# Eozinofīlie (abs.sk.)	0.03 10^9/L	(0.000-0.400)
	BASO% Bazofīlie	0.3 %	(0.00-1.00)
	BASO# Bazofīlie (abs.sk.)	0.02 10^9/L	(0.000-0.100)
	.		
<<	RBC Eritrocīti	2.96 10^12/L	(4.20-5.80)
<<	HGB Hemoglobīns	7.80 g/dL	(14.00-16.00)
<<	HCT Hematokrīts	26.2 %	(39.0-50.0)
	MCV Vidējais eritrocīta tilpums	88.5 fL	(80.00-97.00)
<	MCH Hb vidēja saturs eritrocītā	26.40 pg	(27.00-31.00)
<	MCHC Hb vidēja konc. vienā eritroc.	29.80 g/dL	(31.80-36.00)
>	RDW-SD RBC sadalījuma plašums-SD	58.0 fL	(37.0-54.0)
>	RDW-CV RBC sadalījuma plašums-CV	18.1 %	(11-16)
	.		
	PLT Trombocītu skaits	245 10^9/L	(150-400)
	MPV Vidējais trombocīta tilpums	11.7 fL	(7-12)
	PDW Trombocītu sadalījuma plašums	13.5 fL	(9-17)
	PCT Trombokrīts	0.29 %	(0.17-0.35)
	P-LCR Trombocītu-lielo šūnu attiec.	36.3 %	(13-43)
	.		
	NRBC% Kodolsaturošie RBC	0.3 /100WBC	
	NRBC# Kodolsaturošo RBC (abs.sk.)	0.02 10^9/L	
	.		

Severity Grade

Severity grade*	Grade 1 - Mild	Severity grade 2 - Moderate	Severity Grade 3 – Severe	Severity grade 4 – Life threatening
Anemia	10.5 - 9.5 g/dL	9.4 - 8.0 g/dL	7.9 - 6.5 g/dL	< 6.5 g/dL
Reduced platelets	99,999 - 75,000 /mm^3	74,999 - 50,000 /mm^3	49,999 - 20,000 /mm^3	< 20,000 /mm
Reduced leucocytes	<LLN - 3,000/mm3	<3,000 - 2,000/mm3	<2,000 - 1,000/mm3	< 1,000 /mm3
Absolute neutrophils number	1500 - 1000/mm3	999 - 750/mm3	749 - 500/mm3	<500/mm3

Actions

- **Grade 1 – mild**
  - Close monitoring, consider reducing the dose of Lzd (300 mg per day or 600 mg three times a week).

Grade 2 - moderate

- Close monitoring, consider reducing the dose of Lzd (300 mg per day or 600 mg three times a week); in case of Grade 2 neutropenia, immediately discontinue Lzd. In the case of Grade 2 neutropenia, consider the use of erythropoietin. The drug administration is be resumed in a reduced dose after the toxicity is decreased to Grade 1.

Grade 3 – severe

- Discontinue Lzd immediately. In the case of Grade 3 anemia, consider the use of erythropoietin. The drug administration is be resumed in a reduced dose after the toxicity is decreased to Grade 1.

Grade 4 – life treatening

- Discontinue Lzd immediately. Consider blood transfusion or administration of erythropoietin. The drug is be reintroduced in a reduced dose after the toxicity is decreased to Grade 1.

PROPOSED MANAGEMENT STRATEGY:

1. Severity grades 3 or 4 - immediately discontinue the drug that causes AE; severity grades 1 and 2 - consider reducing the dose.
2. If you suspect that anemia during treatment with linezolid is accompanied by the iron deficiency anemia, you should check the iron reserves in the body, and provide appropriate treatment of the diagnosed iron deficiency .
3. If the test for iron deficiency cannot be performed, empirical iron deficiency therapy can be provided. It should be noted that when taken orally, iron can bind to FQ and reduce its absorption. Iron and FQ should be taken at least 3 hours apart.
4. Ensure regular CBC.

PROPOSED MANAGEMENT STRATEGY :

5. If available, erythropoietin should be considered for management of grade 3 anemia. (Most programs for the management of anemia caused by the toxic effects of linezolid do not use erythropoietin, while according to some evidence, it shows good results.)

6. In case of severe myelosuppression, hospitalize your patient and consider blood transfusion (or the use of erythropoietin).

7. If linezolid is eventually discontinued, the use of additional TB medications should be considered.

Erythropoietin (EPO)

- Treatment with erythropoietin is not intended for patients who require urgent management of anemia (Grade IV severity).
  - In this case, consider blood transfusion.
- To assess treatment response, weekly CBC is required.
- Blood pressure should be checked before treatment initiation and monitored during treatment.
- Treatment with erythropoietin should be discontinued as soon as the level hemoglobin exceeds 12 g /dl.

Thank you for your attention!

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