

Kidney Protective Effects of Acetazolamide for Patients Receiving High Dose Methotrexate: A Systematic Review and Meta-Analysis.

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Characteristic table

BACKGROUND

- High-dose methotrexate (HDMTX) (1 to 12 grams per square meter of body-surface area (g/m^2)) is frequently used in osteosarcoma, acute lymphoblastic leukemia.
- MTX is 90% cleared by the kidneys [2]. The incidence of Acute Kidney Injury (AKI) following HDMTX ranges from 2 to 12%
- Urine alkalization is one of the standard 0 treatments to prevent AKI in patients receiving HDMTX.
- While sodium bicarbonate infusion has been Ο used as the first-line strategy, carbonic anhydrase inhibitors is a promising adjuvant/substitute with advantages such as faster urine alkalization time and avoid fluid overload.
- However, there is limited and incongruent Ο evidence of its efficacy and safety.

OBJECTIVES

- To compare the efficacy and safety of Ο carbonic anhydrase inhibitors to standard treatments in adult patients receiving HDMTX.
- The primary outcome: Incidence of HDMTXrelated AKI

RESULTS

- Among 198 articles retrieved, six 0 observational studies met all eligibility criteria. Four studies with five datasets (totally 558 patients/cycles) had enough data to include their results in the metaanalysis.
- No significant difference between AZL versus 0 standard treatment in AKI rate (OR=0.79, 95% CI 0.48-1.29, P=0.34, I2=0%).
- No significant time difference between the 0 two groups regarding time to urine pH (MD =0.07, 95% CI –1.9 to 2.04, P = 0.95, I2 = 25%).
- AZL did not reduce LOS (MD = 0.75, 95% CI -Ο 0.8 to 2.31, P = 0.34, I2 = 0%).
- The only reported side effect of 0 AZL: hypokalemia (nearly 50% in AZL group) in one study.
- The overall assessed risk of bias was 0 moderate to high. due to the studies' designs, in variable definitions, doses as well as routes of medication administration

Figure 1: PRISMA flowchart



DISCUSSION

- This systematic review and meta-analyses 0 revealed that AZL, co-administered with other alkalization treatments or alone, was not less effective in preventing the toxicities related to HDMTX.
- Because some setbacks could underestimate AZL's protective effects and the evidence of AZL's effectiveness is still not concrete, the practice of using AZL in HDMTX patients need further assessment with a larger sample size. However, AZL is still a promising alternative for patients receiving HDMTX for many reasons.
- Most of the studies showed that AZL was a 0 safe agent for patients receiving HDMTX, with a limited range of side effects such as hypokalemia which could be prevented by oral potassium supplementation

CONCLUSIONS

- This systematic review showed no significant 0 difference between AZL and standard care treatment regarding urine alkalinization time and AKI rate in adult patients receiving HDMTX.
- We are unable to draw conclusions for practice on the use of carbonic acid inhibitors in patients receiving high doses of methotrexate.

The secondary outcomes : Time to achieve Ο urine pH goal, urine output and fluid balance, MTX clearance, liver toxicity rate, and cost effectiveness and length of hospital stay (LOS).

METHODS

- The protocol was registered at PROSPERO Ο (CRD42022352802) in August 2021.
- We included randomized controlled trials or Ο comparative observational studies that enrolled participants 18 years old or older receiving HDMTX.
- We excluded articles irrelevant to the topic 0 and/or did not provide sufficient data regarding doses, recruitment criteria, and follow-up period.
- A comprehensive search was performed on 0 June 27, 2022. Two authors performed the data extraction independently.

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FIGURE 2: Forest plots

	Experimental		Control			Odds Ratio	Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl	
Amanda 2019	2	37	3	39	7.2%	0.69 [0.11, 4.36]		
Amber 2020	12	76	9	41	26.6%	0.67 [0.25, 1.75]		
Amber 2020 B	16	70	9	41	28.7%	1.05 [0.42, 2.66]		
Daniel 2019	12	83	4	43	17.2%	1.65 [0.50, 5.46]		
Mathew 2020	4	68	24	164	20.4%	0.36 [0.12, 1.09]		
Total (95% CI)		334		328	100.0%	0.79 [0.48, 1.29]	•	
Total events	46		49				100	
Heterogeneity: Tau*:	= 0.00; Chi ²	= 3.88	df = 4 (P	= 0.42); I [#] = 0%	L.		10
Test for overall effect	Z = 0.95 (P = 0.34	4)			0.	Favours (AZL + OTs) Favours (control)	10

Meta-analysis forest plots of acute kidney injury incidence of pooled data regardless the route of AZL administration

	AZL and of	ther tream	ents	0	ontroi	l		Mean Difference		Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	\$0	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI	
Amanda 2019	15.4	5.5	37	14.9	6.5	39	33.1%	0.50 [-2.20, 3.20]	2019	•	_
Daniel 2019	4.8	2.2	54	4.8	1.8	12	66.7%	0.00 [-1.18, 1.18]	2019		
Amber 2020	28.9	78.3	76	64.3	175	41	0.1%	-35.40 [-91.79, 20.99]	2020		
Amber 2020 B	21.1	49	70	64.3	175	41	0.1%	-43.20 [-97.98, 11.58]	2020		
Total (95% CI)			237			133	100.0%	0.07 [-1.90, 2.04]			
Heterogeneity: Tau* =	1.15; Chi#=	4.03, df = 3	(P=0.2	6); P= 2	5%					100 50 0 50 1	100
Test for overall effect	Z = 0.07 (P =	0.95)								Favours (AZL+ OTs) Favours (control)	100

Meta-analysis forest plots of time to urine pH goal of pooled data regardless of the route of AZL administration

	AZ	1+01		(Control			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	Year	IV, Random, 95% CI
Amanda 2019	151	193	37	112	76	39	0.1%	39.00 [-27.61, 105.61]	2019	- <u> </u>
Daniel 2019	3.8	5.6	54	3.1	0.9	12	97.1%	0.70 [-0.88, 2.28]	2019	
Amber 2020	127	12.74	70	125.9	41.47	41	1.4%	1.10[-11.94, 14.14]	2020	-
Amber 2020 B	128.3	15.65	76	125.9	41.47	41	1.4%	2.40 [-10.77, 15.57]	2020	+
Total (95% CI)			237			133	100.0%	0.75 [-0.80, 2.31]		•
Heterogeneity: Tau ^a	= 0.00; C	hP=1.3	3, df=	3 (P = 0).72); P	0%				tion to to to
Test for overall effect	t Z = 0.95	6 (P = 0.	34)							Favours [AZL + OTs] Favours [control]

Meta-analysis forest plots of the length of hospital stay from pooled data regardless of the route of AZL administration

We suggest performing a large blinded, 0 randomized, controlled trial to evaluate the potential benefits of this low-cost medication.

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