South Africa National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Oncologic emergencies

MEDICINE REVIEW

1. Executive Summary

Date: 15 March 2019
Medicine (INN): Allopurinol, oral
Medicine (ATC): M04AA01
Indication/s (ICD10 code/s): Prevention of tumour lysis syndrome (TLS) (E88.3)
Patient population/s: Adult cancer patients (Commonly seen with hematologic malignancies; cancers with rapidly growing tumours, particularly acute leukaemia and high-grade lymphoma)
Prevalence of condition/s: Local prevalence data not available; Cochrane review: "Incidence of TLS varies among studies.
A retrospective review of acute lymphoblastic leukaemia, acute myeloid leukaemia, and non-Hodgkin's lymphoma found that the frequency of TLS was 3.4%, 5.2%, and 6.1% (Belgium, The Netherlands, Spain and United Kingdom). The mortality rate of TLS has been estimated to be about 17.5%"[i]
Level of Care: Secondary level – Adult hospital
Prescriber Level: Doctor
Current standard of Care: n/a
Efficacy estimates: n/a (no RCT evidence available, but only a case series study from 1966, *Krakhoff et al, 1966*[ii]
Motivators/reviewers*:* Ms TD Leong; Dr A Sherriff
PTC affiliation: Dr A Sherriff - Free State Provincial PTC

2. Name of author(s)/motivator(s)

Reviewers: Ms TD Leong; Dr A Sherriff

3. Author affiliation and conflict of interest details

Ms TD Leong: National Department of Health, Essential Drugs Programme, Secretariat to the Adult Hospital Level Committee (2017-2020); No conflicts of interest declared.
Dr A Sherriff: HOD Oncology: University of the Free State, Adult Hospital Level Committee (2017-2020); No applicable conflicts of interest.

4. Introduction/ Background

Tumour lysis syndrome (TLS) is a potentially life-threatening emergency that can develop rapidly after the release of intracellular contents such as nucleic acids (which are rapidly converted to uric acid), phosphate, and potassium from lysed malignant cells[iii]. TLS is characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. It can occur spontaneously or soon after initiation of therapy, especially in patients with high-grade malignancies.

For patients at risk for TLS prophylactic management would consists of hydration, therapies that decrease the production of uric acid (e.g., allopurinol) or enzymatically remove it (e.g., rasburicase)[iv v]; as well as avoiding exogenous potassium and phosphorus. Close monitoring is also required to detect metabolic abnormalities before they cause symptoms.

Allopurinol reduces the production of uric acid but has no effect on current uric acid levels. Rasburicase can reduce existing uric acid levels and is also effective when the tumour burden is anticipated to be high. Recently, febuxostat, a non–purine selective inhibitor, was approved by the US Food and Drug Administration (FDA) for chronic management of hyperuricemia in patients with gout[vi],and it is currently being studied in the TLS setting.

Allopurinol inhibits xanthine oxidase, the enzyme that converts hypoxanthine to xanthine and xanthine to uric acid[iii], [and] thus prevent the formation of new uric acid from purines released by cancer cell lysis this reduces the serum and urinary levels of uric acid. In a phase III clinical trial, allopurinol (300 mg/day orally) administered to adults on days 1 to 5 resulted in a response rate (defined as uric acid levels ≤ 7.5 mg/dL for all measurements from days 3 to 7) of 66% (95% CI56% to76%[vii]. When used to prevent uric acid nephropathy from anticancer therapy, it is recommended to administer as high volume of fluids with allopurinol 600 to 800 mg/day orally[iii]. The allopurinol dose must be adjusted in patients with acute kidney injury because it is renally cleared. A decrease in serum and urinary uric acid levels can be expected within 2 to 3 days.

5. Purpose/Objective

Population: Patients with malignancies that have a high risk for tumour lysis syndrome
Intervention: Oral Allopurinol
Comparison: placebo
Outcomes: Prevention and treatment of Tumour lysis syndrome

6. Methods:

a) Data sources and search strategy

i. Cochrane:

[Allopurinol] AND [Tumour lysis syndrome]

- 3 reviews retrieved – all 3 excluded as not related to PICO question

ii. Pubmed:

(((("allopurinol"[MeSH Terms] OR "allopurinol"[All Fields]) AND ("tumour lysis syndrome"[All Fields] OR "tumor lysis syndrome"[MeSH Terms] OR ("tumor"[All Fields] AND "lysis"[All Fields] AND "syndrome"[All Fields]) OR "tumor lysis syndrome"[All Fields])) AND ("adult"[MeSH Terms] OR "adult"[All Fields] OR "adults"[All Fields])) AND ("neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields]) AND "humans"[MeSH Terms]

- 84 articles retrieved; 83 excluded – mix of case reports, narrative reviews, and comparative trials of more current agents (rasburicase and febuxostat) compared to recognized standard of care, allopurinol. 1 article – ASCO Guidelines (Coiffer et al, 2016) considered relevant.

iii. *Google scholar*

- **Observational Study:** Case series study by Krakoff et al, 2016

b) Evidence synthesis

Table 1 Summary of included studies/systematic reviews and meta-analysis

Author, date	Type of study	n	Population	Comparators	Outcomes: primary and secondary	Effect sizes	Comments
Observational study							
Krakoff et al, 1996	Observational study (Case series study)	106 patient cases	Mostly patients with lymphoma and leukemia	Patients not receiving allopurinol	Serum uric acid determinations were performed by the colorimetric method of Archi-bald. Urine uric acid was measured by ultra- violet spectropliotometry using the method of Dubbs, Davis and Adams. In selected urine specimens total non-uric-acid oxypurines were determined by measuring the increase in absorbance at 292 m after treatment with xanthine oxidase.	Allopurinol, oral, 300 to 800 mg daily produced a decrease in serum uric acid in all but one patient. The single exception was a patient with renal insufficiency and intestinal obstruction, possibly affecting absorption of allopurinol and altering extrarenal disposition of uric acid.	Small observational study done in 1996 – informing guideline recommendations of allopurinol to prevent uric acid in tumour lysis syndrome. Subsequently, other agents have become available but is cost prohibitive.
Guidelines							
ASCO Guidelines: Coiffer et al, 2016[viii]	Guidelines for the the prevention and management of patients at risk of developing TLS.	**Recommendations for management of hyperuricaemia:** • *Hydration. M*ainstay of prophylaxis *for* and treatment of TLS remains adequate hydration, with the exception of patients presenting with renal failure or oliguria. Try and achieve equal fluid intake and urinary output, if at all possible. • *Alkalinization.* Not recommended as there is no unequivocal evidence of efficacy; and alkalinization may increase the risk of precipitation of calcium phosphate crystals. Sodium bicarbonate may be indicated in patients with co-morbid metabolic acidosis, guided by individual institutional protocols. • *Antihyperuricaemic agents:* o **Allopurinol:** Consider as prophylaxis in patients with a medium risk of developing TLS (baseline uric acid >450 mmol/l). Contra-indicated in patients allergic to allopurinol. Prevents prevents the formation of uric acid and does not reduce uric acid produced. Dose-adjust in renal impairment and monitor for drug-drug interactions. o **Rasburicase:** Recommended as second line option if poor/no repsonse to allopurinol and as prophylaxis in patients considered to be at high risk of developing TLS (baseline uric acid >450 mmol/l)				Industry and NGO funding. Many of the recommendations are based upon expert opinion and may differ from the dosages approved by Regulatory Authorities. Rasburicase is currently not available on the South African market. As all these patients need to referred to an oncology unit for adequate management.

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident: [ ] Not confident: [ ] Uncertain: [X]	This is standard practice; and RCT evidence is limited.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms: [ ] Harms outweigh benefits: [ ] Benefits = harms or Uncertain: [X]	This is standard practice; and RCT evidence is limited.
VALUES & PREFERENCES / ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the outcomes?** Minor: [ ] Major: [ ] Uncertain: [X] **Is the option acceptable to key stakeholders?** Yes: [ ] No: [ ] Uncertain: [X]	
RESOURCE USE	**How large are the resource requirements?** More intensive: [ ] Less intensive: [ ] Uncertain: [x]	**Cost of medicines/ month:** Medicine: Allopurinol, oral 100 to 300 mg 8 hrly — Cost (ZAR)*: 47.15 to 41.85 * Contract circular RT289-2019: Allopurinol 300mg tab = R0.465; Weighted average price of allopurinol 100mg tab = R0.524
EQUITY	**What would be the impact on health inequity?** Yes: [ ] No: [ ] Uncertain: [X]	
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes: [x] No: [ ] Uncertain: [ ]	.

Type of recommendation	We recommend against the option or for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	☐	[X]	☐

Recommendation: Based on this evidence review, the Adult Hospital Level Committee recommends oral for prevention of tumour lysis syndrome.

Rationale: Standard practice and there is a paucity of high quality RCT evidence for allopurinol for the prevention of tumour lysis syndrome. Allopurinol is currently used as the standard of care/comparator in clinical intervention trials.

Level of Evidence: III Case report [ii], Standard of care as suggested by Guidelines [viii] [ix]

Review indicator:

Evidence of efficacy: [ ] Evidence of harm: [X] Price reduction: [ ]

VEN status:

Vital: [ ] Essential: [X] Necessary: [ ]

NEMLC MEETING OF 5 DECEMBER 2019
NEMLC accepted the proposal as recommended by the Adult Hospital Level Committee, above.

Monitoring and evaluation: n/a

Research priorities : Epidemiology research of Tumour Lysis Syndrome in South Africa.

References:

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[iv] Howard Scott C, Jones Deborah P, Pui Ching-Hon. The tumor lysis syndrome. The New England journal of medicine. 2011;364:1844–1854

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