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Department:
Health
REPUBLIC OF SOUTH AFRICA

SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 21: ONCOLOGIC EMERGENCIES
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2017 -2019)

Background

Previous editions of the Adult Hospital Level STGs and EML included a chapter for oncologic medicines to facilitate accessibility of bleomycin, hydroxyurea, tamoxifen and vincristine at secondary level of care. The rationale was that certain oncological conditions (e.g.: Kaposi sarcoma) may be managed at secondary level of care, in consultation with a specialist. The Standard Treatment Guideline further recommended that this does not restrict down-referral of oncology agents (according to Provincial guidelines) for continuation of care of patients who have been stabilised.

However, as each Province determines and authorises the oncology services to be provided at specific secondary or regional level institutions, the Adult Hospital Level Committee recommends that the objective of this chapter be amended. Furthermore, prevalence of Kaposi sarcoma is decreasing due to the roll out of antiretroviral therapy and severe cases are generally managed at tertiary level of care.

General

Objective: The chapter has been amended from a list of oncology medicines to management of oncologic emergencies and management of associated common side-effects.

Access to oncologic agents at secondary/regional level: Down referral mechanisms and Provincial Pharmaceutical and Therapeutics Committee are available mechanisms to ensure access of oncologic agents at sites approved by Provinces.

Chapter layout:

21.1 Oncological emergencies
- 21.1.1 Metabolic emergencies
  - 21.1.1.1 Hypercalcemia of malignancy
  - 21.1.1.2 Syndrome of inappropriate antidiuretic hormone (ADH)
  - 21.1.1.3 Tumor lysis syndrome
- 21.1.2 Haematologic emergencies
  - 21.1.2.1 Febrile neutropenia
  - 21.1.2.2 Hyperviscosity syndrome
- 21.1.3 Structural emergencies
  - 21.1.3.1 Epidural spinal cord compression
  - 21.1.3.2 Malignant pericardial effusion
  - 21.1.3.3 Superior vena cava syndrome

21.2 Side effects from oncologic treatment agent
- 21.2.1 Diarrhoea
- 21.2.2 Extravasations
- 21.2.3 Constipation

21.3 Side effects from radiation
- 21.3.1 Radiation mucositis
- 21.3.2 Wet desquamation of skin
- 21.3.3 Radiation and chemotherapy-induced pneumonitis
- 21.3.4 Radiation proctitis
- 21.3.5 Radiation cystitis

21.4 Side effect from chronic pain medication
- 21.4.1 Constipation
- 21.4.2 Nausea & vomiting
- 21.4.3 Depression

Medicine recommendations, with supporting evidence and rationale are listed below. Kindly review the medicine amendments in the context of the chapter for oncologic emergencies

SECTION	MEDICINE	ADDED/DELETED/AMENDED
21.1 ONCOLOGIC EMERGENCIES		
21.1.1 Metabolic emergencies		
21.1.1 Hypercalcemia of malignancy	n/a	Cross referenced to section 8.9: Hypercalcaemia, including primary hyperparathyroidism
21.1.1.2 Syndrome of inappropriate antidiuretic hormone (ADH)	n/a	Cross referenced to section: 7.2.4 Hyponatraemia
21.1.1.3 Tumour lysis syndrome	Sodium chloride 0.9%, IV	Added
	Dextrose 5%, IV	Not added
	Sodium bicarbonate, IV	Not added
	Allopurinol, oral	Added
21.1.2 Haematologic emergencies		
21.1.2.1 Febrile neutropenia	n/a	Cross referenced to section 2.8: Febrile neutropaenia
21.1.2.2 Hyperviscosity syndrome	n/a	n/a
21.1.3 Structural emergencies		
21.1.3.1 Epidural spinal cord compression	Dexamethasone, IV	Added
21.1.3.2 Malignant pericardial effusion	Sodium chloride 0.9%, IV	Not added
	Dexamethasone, IV	Not added as a pre-referral dose (high dose)
21.1.3.3 Superior vena cava syndrome	Sodium chloride 0.9%, IV	Added
	Corticosteroids	Added (specialist consultation)
21.2 Side effects from oncology treatment agent		
21.2.1 Diarrhoea	n/a	Cross referenced to section 1.3.3: Diarrhoea, acute non-inflammatory.
21.2.2 Extravasations	Clindamycin, oral	Added, where secondary infection is suspected
21.2.3 Constipation	n/a	Cross referenced to section 2.8: Constipation and Primary Health Care chapter: Medicines for palliative care; section 22.1.1: Constipation.
21.3 Side effects from radiation and chemotherapy		
21.3.1 Radiation mucositis	Saline mouth rinse	Added
21.3.2 Wet desquamation of skin	n/a	n/a
21.3.3 Radiation and chemotherapy induced pneumonitis	Prednisone, oral	Added
21.3.4 Radiation proctitis	Topical steroids	Not added as pre-referral protocol
21.3.5 Radiation cystitis	Mist potassium citrate	Not added
21.4 Side effect from chronic pain medication		
21.4.1 Constipation	n/a	Cross-referenced to section 25.1.3: Treatment of adverse effects of chronic opioid use.
21.4.2 Nausea & vomiting	n/a	Cross-referenced to section 25.1.3: Treatment of adverse effects of chronic opioid use.
21.4.3 Depression	n/a	Cross-referenced to Primary Health Care chapter: Medicines for palliative care; section 22.2.3: Depression.

21.1.1.3 TUMOUR LYSIS SYNDROME

This Standard Treatment Guideline (STG) was developed, aligned with Clinical Practice Guideline[1], and assessed using the AGREE II instrument.

Sodium chloride 0.9%, IV: *added*
Dextrose 5%, IV: *not added*
Dextrose 5%, IV was not added to the STG as a resuscitation fluid, as sodium chloride 0.9% recommended consistent with the rest of the adult STGs. If patient is hypernatraemic or fluid overloaded, a specialist be consulted.

Sodium bicarbonate, IV**:** *not added*
Sodium bicarbonate, IV as a urinary alkaliniser not recommended as there was reported to be conflicting evidence for this intervention in tumour lysis syndrome.

Allopurinol, oral**:** *added*
Allopurinol has been standard of care prior to 1996 for prevention of tumour lysis syndrome, refer to the medicine review, allopurinol for tumour lysis (March 2019):

Allopurinol for Tumour Lysis Syndrc

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on this evidence review, the Adult Hospital Level Committee recommended oral allopurinol 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[2], Standard of care as suggested by Guidelines [3][4]

Guidelines (mentioned above) recommends allopurinol to prevent tumour lysis syndrome at a dose of 200–400 mg/m2/day in 1–3 divided doses for adults, up to a maximum of 800 mg daily, prior to starting chemotherapy. It is noted that allopurinol is available on the South African market as a "300 mg" tablet formulation. Maximum dose recommended as "900 mg" daily for pragmatic purposes. The STG recommends pre-referral dosing.
Level of Evidence: III Guidelines, Expert opinion

21.1.3.1 EPIDURAL SPINAL CORD COMPRESSION

Dexamethasone, IV: *added*
Corticosteroids has long-standing standard of care of care, prior to 1996 for preventing neurological decline due to metastatic spinal cord compression (MSCC); refer to medicine review (dexamethasone oral/IV for MSCC, November 2019):

[1] Coiffier B, Altman A, Pui CH, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol. 2008 Jun 1;26(16):2767-78. https://www.ncbi.nlm.nih.gov/pubmed/18509186
[2] Krakoff IH. Use of allopurinol in preventing hyperuricemia in leukemia and lymphoma. Cancer. 1966 Nov;19(11):1489-96. https://www.ncbi.nlm.nih.gov/pubmed/5925255
[3] Coiffier B, Altman A, Pui CH, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol. 2008 Jun 1;26(16):2767-78. https://www.ncbi.nlm.nih.gov/pubmed/18509186
[4] Jones GL, Will A, Jackson GH, Webb NJ, Rule S; British Committee for Standards in Haematology. Guidelines for the management of tumour lysis syndrome in adults and children with haematological malignancies on behalf of the British Committee for Standards in Haematology. Br J Haematol. 2015 Jun;169(5):661-71. https://www.ncbi.nlm.nih.gov/pubmed/25876990

Steroids for Spinal Cord Compression_A

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation

Based on this evidence review, the Adult Hospital Level Committee recommends moderate dose corticosteroids to reduce inflammation, oedema and pain in metastatic spinal cord compression; either with/without surgery or radiation. NICE[5] and Canadian guidelines[6] recommend starting with a loading dose of at least 16 mg, followed by doses of 16 mg per day.

Rationale: Limited evidence of low quality suggests that moderate dose corticosetroids may be benificial in enhancing ambulation, long-term survival, reducing pain, improving urinary incontinence ; but there is uncertainty regarding the optimal dose. However, high doses of steroids are associated with a higher risk of adverse effects (such as perforated gastric ulcer, psychoses and deaths due to infection).

Level of Evidence: III Systematic review of low quality RCTs

External comment was received from a stakeholder, to recommend high dose dexamethasone as vasogenic oedema causes spinal cord damage due to limited space to expand. However, evidence suggests that there is no benefit of initial high dose vs conventional moderate dose corticosteroid (refer to medicine review, above).

Level of Evidence: III Systematic review of low quality RCTs[7]

21.1.3.2 MALIGNANT PERICARDIAL EFFUSION

Sodium chloride, IV: *not added*

Sodium chloride, IV was not recommended in this clinical setting, as patient with hypotension and tamponade should first be tapped to determine the underlying aetiology.

Level of Evidence: III Expert opinion

Dexamethasone, IV: *not added as a pre-referral dose (high dose)*

External comment received (without supporting evidence) that high dose dexamethasone may be of value as a pre-referral recommendation. However, the European Society of Cardiology recommends that systemic corticosteroid therapy be restricted to connective-tissue diseases, autoreactive pericarditis, or uraemic pericarditis[8]. The STG recommends that all patients should be referred for definitive therapy.

Level of Evidence: III Guidelines, Expert opinion

21.1.3.3 SUPERIOR VENA CAVA SYNDROME

Sodium chloride, IV: *added*

Sodium chloride, IV recommended as a resuscitation fluid.

[5] NICE. Metastatic spinal cord compression in adults, November 2008. https://www.nice.org.uk/guidance/cg75

[6] Loblaw DA, Mitera G, Ford M, Laperriere NJ. A 2011 updated systematic review and clinical practice guideline for the management of malignant extradural spinal cord compression. Int J Radiat Oncol Biol Phys. 2012 Oct 1;84(2):312-7. https://www.ncbi.nlm.nih.gov/pubmed/22420969

[7] George R, Jeba J, Ramkumar G, Chacko AG, Tharyan P. Interventions for the treatment of metastatic extradural spinal cord compression in adults. Cochrane Database Syst Rev. 2015 Sep 4;(9):CD006716. https://www.ncbi.nlm.nih.gov/pubmed/26337716

[8] Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias G, Bogaert J, Brucato A, Gueret P, Klingel K, Lionis C, Maisch B, Mayosi B, Pavie A, Ristic AD, Sabaté Tenas M, Seferovic P, Swedberg K, Tomkowski W; ESC Scientific Document Group . 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC)Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2015 Nov 7;36(42):2921-2964. https://www.ncbi.nlm.nih.gov/pubmed/26320112

Corticosteroids: *added (specialist consultation)*
Despite patient referrals for directed management on histological diagnosis; delay in referral may occur and thus, corticosteroids may considered in consultation with a specialist
Level of Evidence: III Expert opinion

21.2.2 EXTRAVASATIONS

Clindamycin, oral: *added*
This was recommended for "*patients with larger areas of erythema and tenderness extending beyond the insertion site, where secondary infection is suspected*".
Rationale: The Adult Hospital Level Committee considered that the recommendation of clindamycin for extravasation due to oncologic treatment agents, where secondary infection is present, describes a favourable risk-benefit assessment of neutropaenic oncologic patients from an antibiotic stewardship perspective. This was aligned with section 9.1.1: Intravascular catheter infections.
Level of Evidence: III Expert opinion, Guidelines[9] [10], pharmacokinetic study[11]

21.3.1 RADIATION MUCOSITIS

Saline mouth rinse: *added*
A small randomised study[12] showed that radiation-induced oral mucositis symptoms were no different between patients receiving standard of care (education of mouthwashes with boiled water for 3-or 4-hr intervals and after meals vs the saline rinse education programme). However, the saline rinse and education programme promoted better physical and social-emotional QOL in oral cavity cancer patients receiving RT/CCRT. Despite the limited evidence of low quality, it was found reasonable to recommend saline mouth rinses which is standard practice.
Level of Evidence: III Disease oriented study, Standard of care

21.3.3 RADIATION AND CHEMOTHERAPY INDUCED PNEUMONITIS

Note that various chemotherapy agents may also cause chemotherapy-induced pneumonitis[13].

Prednisone, oral: *added*
Prednisone is long-standing standard of care prior to 1996 for radiation and chemotherapy-induced pneumonitis; refer to medicine review (Prednisone for pneumonitis, November 2019):

Prednisone for Pneumonitis_AdultR

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on this review, the Adult Hospital Level Committee recommended prednisone, oral for management of acute radiation pneumonitis.
Rationale: Limited evidence in the literature for preventing, mitigating and treating acute and late radiation induced lung injury. Mainstay of therapy and was found to be probably biologically plausible,

[9] South African Antibiotic Stewardship Programme. A Pocket Guide to Antibiotic Prescribing for Adults in South Africa, 2015.http://www.fidssa.co.za/images/SAASP_Antibiotic_Gudidelines_2015.pdf
[10] SAMF, 2016
[11] Bouazza N, Pestre V, Jullien V, Curis E, Urien S, Salmon D, Tréluyer JM. Population pharmacokinetics of clindamycin orally and intravenously administered in patients with osteomyelitis. Br J ClinPharmacol. 2012 Dec;74(6):971-7.http://www.ncbi.nlm.nih.gov/pubmed/22486719
[12] Huang BS, Wu SC, Lin CY, Fan KH, Chang JT, Chen SC. The effectiveness of a saline mouth rinse regimen and education programme on radiation-induced oral mucositis and quality of life in oral cavity cancer patients: A randomised controlled trial. Eur J Cancer Care (Engl). 2018 Mar;27(2):e12819. https://www.ncbi.nlm.nih.gov/pubmed/29315944
[13] McDonald S, Rubin P, Phillips TL, Marks LB. Injury to the lung from cancer therapy: clinical syndromes, measurable endpoints, and potential scoring systems. Int J Radiat Oncol Biol Phys. 1995 Mar 30;31(5):1187-203. https://www.ncbi.nlm.nih.gov/pubmed/7713782

as suggested in Guidelines and case reports.
Level of Evidence: Standard of care as suggested by Guidelines[14], Case Reports[15] [16]

External comment was received from stakeholder to increase the dose of prednisone. However, the current recommendation is aligned with Guidelines.
Level of Evidence: III Guidelines[17], Standard of care

21.3.4 RADIATION PROCTITIS

Referral
Topical steroids: *not added as pre-referral protocol*
External comment received indicating that topical steroids may be of value when the patient is referred to a radiation oncology centre. However, management would be determined at the referral centre.
Level of Evidence: III Expert opinion

21.3.5 RADIATION CYSTITIS

Mist potassium citrate, oral: *not added*
No available evidence for mist potassium citrate in the management of radiation cystitis could be retrieved.

Report prepared by TD Leong: Secretariat to the Adult Hospital Level Committee (2017-2020)
- ***Note**: Information was sourced from NEMLC ratified minutes and NEMLC-approved documents.*

[14] Small W Jr, Woloschak G. Radiation toxicity: a practical guide. Introduction. Cancer Treat Res. 2006;128:3-5. https://www.ncbi.nlm.nih.gov/pubmed/16335011
[15] Ta V, Aronowitz P. Radiation pneumonitis. J Gen Intern Med. 2011 Oct;26(10):1213-4. https://www.ncbi.nlm.nih.gov/pubmed/21538170
[16] Conway JL, Long K, Ploquin N, Olivotto IA. Unexpected Symptomatic Pneumonitis Following Breast Tangent Radiation: A Case Report. Cureus. 2015 Oct 22;7(10):e363. https://www.ncbi.nlm.nih.gov/pubmed/26623218
[17] Small W Jr, Woloschak G. Radiation toxicity: a practical guide. Introduction. Cancer Treat Res. 2006;128:3-5. https://www.ncbi.nlm.nih.gov/pubmed/16335011