National Essential Medicine List
Tertiary/Hospital Medication Review Process
Component: Oncology

Medication Name: Cisplatin plus Paclitaxel

Indications: Advanced/metastatic cervical carcinoma (C53.0 – C53.9)

Context:
Cervical carcinoma is the second most common malignancy amongst women in South Africa with nearly 6000 new cases per year, more than half will die of this disease[1]. Patient who relapse, or who have persistent or metastatic disease, are managed with palliative chemotherapy to improve outcomes and quality of life.

Effective treatment in the metastatic setting is cisplatin-based chemotherapy either as monotherapy or in combination with other agents. Cisplatin adverse-effects include myelosuppression; renal dysfunction; emesis (highly emetogenic chemotherapy) and peripheral neuropathy; especially at doses of $\geq$75mg/m^2.

Studies comparing monotherapy to platinum-based doublets have shown that combination with paclitaxel has a higher response rate than single agent cisplatin or in combination with vinorelbine, gemcitabine or topotecan. Carboplatin may substitute for cisplatin if the glomerular filtration rate is 30ml-59ml/min.

Quality of evidence:
Level 1 evidence – Phase III randomised clinical trials

Clinical efficacy:

Author, date	Type of study	n	Population	Comparators	Primary outcome	Effect sizes		
						Overall response rate (ORR)	Overall survival (OS)	Progression free survival (PFS)
GOG 169; Moore 2004[2]	Phase III, randomised trial	264	Advanced, recurrent or persistent cervical cancer	Cisplatin vs Cisplatin/ Paclitaxel	Overall response rates (ORR)	19% vs 36% (p=0.002)	Median 8.8 vs 9.7 months (NS)	Median 2.8 vs 4.8 months (p<0.001)

Safety: Increased grade 3 to 4 anaemia (13% vs 27.6%); neutropaenia (3.1% vs. 66.6%) but not febrile neutropaenia (0% vs. 0.8%) in combination arm.

Author, date	Type of study	n	Population	Comparators	Primary outcome	ORR	OS (HR; 95% CI)	PFS (HR; 95% CI)
GOG 204; Monk 2009[3]	Phase III, randomised trial	513	Advanced, recurrent or persistent cervical cancer	Cisplatin/Paclitaxel vs. Cisplatin/Vinorelbine; Cisplatin/Gemcitabine & Cisplatin/Topotecan	Overall survival (OS)	29.1% vs. 25.9%; 22.3%; 23.4%. (NS)	PC vs VC (12.9 vs 10.3 month HR 1.15; 0.97-1.67) PC vs. GC (12.9 vs 10.3 month HR 1.32; 0.91-1.92 PC vs TC (12.9 vs 10 month HR 1.26; 0.86-1.82)	PC vs VC (5.8 vs 4.7 months; HR 1.36; 0.97-1.9) PC vs GC (5.8 vs 4.6 months; HR 1.39; 0.99-1.96 PC vs TC (5.8 vs 4.0 months; HR 1.27; 0.9-1.78)

Note: Closed early due to futility
Safety: The arms were comparable with respect to toxicity except for leucopenia, neutropenia, infection, and alopecia.

Cisplatin-based chemotherapy:

Table 2. Combination regimens tested in phase III studies for the treatment of advanced stage (IVB), recurrent, or persistent cervical cancer

Trial	Regimen	RR (%)	OS (months)	PFS (months)
GOG 110 [18]	Cisplatin 50 mg/m^2	17.8	8	3.2
	Cisplatin 50 mg/m^2 + DBD 180 mg/m^2	21.1	7.3	3.3
	Cisplatin 50 mg/m^2 + ifosfamide 5 g/m^2 + mesna	31.1	8.3	4.6
GOG 149 [19]	Cisplatin 50 mg/m^2 + ifosfamide 5 g/m^2	32	8.5	4.6
	Cisplatin 50 mg/m^2 + ifosfamide 5 g/m^2 + bleomycin 30 units	31.2	8.4	5.1
GOG 169 [20]	Cisplatin 50 mg/m^2	19	8.8	2.8
	Cisplatin 50 mg/m^2 + paclitaxel 135 mg/m^2	36	9.7	4.8
GOG 179 [21]	Cisplatin 50 mg/m^2	13	6.5	2.9
	Cisplatin 50 mg/m^2 + topotecan 0.75 mg/m^2 days 1–3	26	9.4	4.6
	MVAC	NA	NA	NA
GOG 204 [22]	Cisplatin 50 mg/m^2 + paclitaxel 135 mg/m^2	29.1	12.9	5.8
	Cisplatin 50 mg/m^2 + topotecan 0.75 mg/m^2 days 1–3	23.4	10.3	4.7
	Cisplatin 50 mg/m^2 + gemcitabine 1000 mg/m^2	22.3	10.3	4.6
	Cisplatin 50 mg/m^2 + vinorelbine 30 mg/m^2	25.9	10	4.0

Recommendation:
Allow the use of combination chemotherapy with cisplatin and paclitaxel for patients who are:

1. Newly diagnosed with advanced/metastatic disease
2. Patients who are > 12 months from primary chemoradiation prior to relapse/distant disease.

Rationale:

1. Significantly higher response rate and progression free survival for cisplatin/paclitaxel compared to cisplatin monotherapy.
2. Slightly higher response rate, progression free survival and overall survival for cisplatin/paclitaxel compared to other cisplatin doublets.
3. Cisplatin/paclitaxel is international standard of care.

Date: June 2019

Review indicators: None

References:

1. Cancer in South Africa: Full Report 2014. www.ncr.ac.za
2. *David H. Moore, John A. Blessing, Richard P. McQuellon, Howard T. Thaler, David Cella, Jo Benda,David S. Miller, George Olt, Stephanie King, John F. Boggess, and Thomas F. Rocereto.* Phase III Study of Cisplatin With or Without Paclitaxel in Stage IVB, Recurrent, or Persistent Squamous Cell Carcinoma of the Cervix: A Gynecologic Oncology Group Study. *J Clin Oncol2004; 22: 3113-3119.*
3. *Bradley J. Monk, Michael W. Sill, D. Scott McMeekin, David E. Cohn, Lois M. Ramondetta,, Cecelia H. Boardman, Jo Benda, and David Cella.* Phase III Trial of Four Cisplatin-Containing Doublet Combinations in Stage IVB, Recurrent, or Persistent Cervical Carcinoma: A Gynecologic Oncology Group Study. *J Clin Oncol* 2009; 27*: 4649-4655.*