Regimen Monograph

A - Regimen Name

CISPPACL+BEVA Regimen

CISplatin-paclitaxel-bevacizumab

Disease Site

Gynecologic
Cervix

Intent

Palliative

Regimen Category

Evidence-Informed :

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses

For the treatment of patients with metastatic, recurrent or persistent cervical cancer of all histologic subtypes (except small cell), who have ECOG performance status of 0 or 1 (see NDFP for detailed funding criteria).

Supplementary Public Funding

bevacizumab
New Drug Funding Program (Bevacizumab (Biosimilar) - Metastatic (Stage IVB), Persistent, or Recurrent Carcinoma of the Cervix)

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B - Drug Regimen

Different bevacizumab products are **not interchangeable**.

PACLitaxel	175 mg /m²	IV over 3 hours	Day 1
CISplatin	50 mg /m²	IV	Day 1 (after paclitaxel)
bevacizumab	15 mg /kg	IV	Day 1

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

Until disease progression or unacceptable toxicity.

(CISPPACL+BEVA is usually given for 6 cycles. May be continued beyond 6 cycles for patients with ongoing benefit and without unacceptable side effects.)

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate

Other Supportive Care:
Also refer to CCO Antiemetic Summary

Standard regimens for cisplatin premedication and hydration should be followed. Refer to local guidelines.

Paclitaxel: Patients should be pretreated with a corticosteroid as well as an antihistamine and a H2 blocker.

For example: dexamethasone 20mg PO 12 & 6 hours OR 20mg IV 30 minutes before paclitaxel, diphenhydramine 50mg IV 30 minutes before paclitaxel and ranitidine 50mg IV 30 minutes before paclitaxel.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. Bevacizumab should not be initiated in patients with recurrent hemoptysis, uncontrolled hypertension or wounds that require healing. Prior to treatment, a dental evaluation should be performed and major dental procedures completed. May consider hypersensitivity prophylaxis (see section D for examples) for patients who have had prior mild hypersensitivity reactions to bevacizumab and are continuing on bevacizumab-only therapy.

Dosage with toxicity

Do not start a new cycle until ANC ≥ 1.5 x 10^9/L and platelets ≥ 100 x 10^9/L. Reduced doses should not be re-escalated.

Dose levels:

Dose level	Cisplatin (mg/m2)	Paclitaxel (mg/m2)	Bevacizumab (mg/kg)
0	50	175	15
-1	37.5	140	15
-2	25	105	15

Hematologic toxicity	Cisplatin	Paclitaxel	Bevacizumab
Febrile neutropenia or Grade 4 neutropenia for > 7d	No change	↓ 1 dose level, consider adding G-CSF for subsequent cycles if recurs*	No change
Grade 4 thrombocytopenia or thrombocytopenic bleeding	No change	↓ 1 dose level	Hold

*If recurs despite addition of G-CSF, reduce a second dose level

Hypersensitivity reaction:

Reaction	Paclitaxel	Bevacizumab
Mild (e.g. mild flushing, rash, pruritus)	Possible to complete the infusion under close supervision	May stop the infusion. Give diphenhydramine and corticosteroid if indicated. Resume infusion at slower rate under close supervision.

Moderate (e.g. moderate rash, flushing, mild dyspnea, chest discomfort, mild hypotension)	Stop the infusion and give diphenhydramine 25-50 mg IV and methylprednisolone 125 mg IV. Once symptoms have resolved, resume infusion at a rate of 10% of original rate for 15 minutes, then at 25% of original rate for 15 minutes, and if no further symptoms develop, continue at original rate until infusion is complete.	Stop the infusion and hold for remainder of the day. Give diphenhydramine and corticosteroid, or other supportive measures if indicated. Consider discontinuing bevacizumab. If re-challenge on a different treatment day, use slower infusion rate.
Severe (e.g. one or more of: respiratory distress requiring treatment, generalized urticaria, angioedema, hypotension requiring therapy)	Stop the paclitaxel infusion and give diphenhydramine and methylprednisolone as above. Use epinephrine or bronchodilators if indicated. Discontinue. Do not re-challenge.	Stop the infusion and give diphenhydramine and corticosteroid. Use epinephrine or bronchodilators if indicated. Discontinue. Do not re-challenge.

Non-hematologic toxicities

Any grade	Grade 3	Grade 4	Bevacizumab action	Paclitaxel/ cisplatin action
Uncontrollable hypertension*			Hold*	Consider hold or discontinue
Delayed wound healing; Surgery**				
Proteinuria ≥2g/24 hours***				
Wound dehiscence; Necrotizing fasciitis			Discontinue	Consider hold or discontinue
Tracheo-esophageal fistula, other non-GI fistulae; GI perforation		Any internal fistula		
Nephrotic syndrome; non recovery of proteinuria ≥2g/24 hours	Hypertension (not controlled with medical managment)	Hypertension		
Severe Hypersensitivity				
PRES/RPLS				
Arterial thromboembolism	Pulmonary embolism	Venous thromboembolism (including pulmonary embolism)		
Symptomatic cardiac failure				
Recurrent hemoptysis > 2.5mL; Intracranial bleeding	Bleeding (any)	Bleeding (any)		
Grade 2 neuropathy or ototoxicity			No change	↓ 2 dose levels
	Grade 3 neuropathy or ototoxicity	Grade 4 neuropathy or ototoxicity	No change	Hold both drugs until recovery to ≤ grade 1

Any grade	Grade 3	Grade 4	Bevacizumab action	Paclitaxel/ cisplatin action
				If no recovery after a 2 week delay, discontinue If recovers, restart with ↓ 2 dose levels
		2 successive episodes of Grade 4 nausea/vomiting	No change	↓ 1 dose level for cisplatin
	Other non-hematologic	Other non-hematologic	No change	Consider dose reduction
Grade 2 or greater nephrotoxicity			No change	Hold cisplatin[#]
Grade 2 or greater hepatotoxicity			No change	Hold paclitaxel[#], then resume at ↓ 1 dose level

*If held for 3 weeks, discontinue bevacizumab and continue chemotherapy. If held 4 or more weeks, discontinue treatment.

**For 28 days PRIOR (if surgery elective) and AFTER major surgery, or until wound healed

***May restart when < 2g/24hrs. If held more than 2 months, discontinue bevacizumab.

[#]Hold until non-hematologic toxicity ≤ grade 1 and SrCr < 1.5 mg/dL (133 umol/L)

Hepatic Impairment

Patients with bilirubin > 1.5 x ULN were excluded from the clinical trial.

Bilirubin		AST/ALT	Paclitaxel	Cisplatin	Bevacizumab
1-2 x ULN			no change	no change	no change
>2-3 x ULN	or	2-5 x ULN	↓ 1 dose level	no change	no change
>3 x ULN	or	> 5 x ULN	discontinue	no change	no change

Renal Impairment

Creatinine Clearance (mL/min)	Paclitaxel (% previous dose)	Cisplatin (% previous dose)	Bevacizumab
>60	no change	no change	no change
46-60	no change	75%	no change
30-45	no change	50%	no change
<30	no change	discontinue	no change

Dosage in the elderly

Use with caution; patients > 65 years old have an increased risk of arterial thrombotic events as well as myelosuppression, fatigue, proteinuria, hypertension, dysphonia and GI effects.

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F - Adverse Effects

Refer to PACLitaxel, CISplatin, bevacizumab drug monograph(s) for additional details of adverse effects

Increased rates of thromboembolism and fistulas were reported in cervical cancer patients in clinical trials.

Most Common Side Effects	Less Common Side Effects, but may be Severe or Life Threatening
• Nausea and vomiting (may be severe) • Alopecia • Peripheral neuropathy (may be severe) • Musculoskeletal pain • Hypertension (may be severe) • Hypersensivity • Ovarian failure • Proteinuria (may be severe) • Nephrotoxicity (may be severe) • Hearing impairment (may be severe) • Myelosuppression +/- infection, bleeding (may be severe) • Hemorrhage (may be severe) • Diarrhea (may be severe) • Increased LFTs (may be severe) • Edema • Insomnia • Mucositis • Fatigue • Anorexia • Constipation • Dysguesia • Headache • Rash (may be severe) • Eye disorders • Venous thromboembolism (may be severe) • Electrolyte abnormalities	• Arterial thromboembolism • Cardiotoxicity, arrhythmia • Pulmonary hypertension • Hemolytic uremic syndrome • Vasculitis • Secondary malignancy • GI perforation/obstruction\ • Fistulas (GI and non-GI) • Pancreatitis • Pneumonitis • Delayed wound healing • Necrotizing fasciitis • Osteonecrosis (jaw, other) • PRES, seizure • Cystoid macular edema • Secondary malignancy • Encephalopathy

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G - Interactions

Refer to PACLitaxel, CISplatin, bevacizumab drug monograph(s) for additional details

- Give cisplatin after paclitaxel when given in combination (increased toxicity and reduced efficacy if paclitaxel given after)
- Use with caution with bisphosphonates and anti-angiogenic drugs given increased risk of ONJ
- Avoid or monitor closely with aminoglycosides and other nephrotoxic drugs, including diuretics

- Monitor closely with phenytoin; phenytoin dosage adjustment may be required
- Monitor INR in patients receiving warfarin; warfarin dosage adjustment may be required.
- Use with caution with anthracyclines or thoracic radiation; this may increase the risk of cardiotoxicity
- Concurrent use with radiation may increase the risk of radiation pneumonitis
- Caution and monitor with CYP3A4 inducers (e.g. phenytoin, St. John's wort) and inhibitors (e.g. azole antifungals, macrolide antibiotics)
- Caution and monitor with CYP2C8 inducers (e.g. phenobarbital) and inhibitors (e.g. gemfibrozil, monteleukast)

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H - Drug Administration and Special Precautions

Refer to PACLitaxel, CISplatin, bevacizumab drug monograph(s) for additional details

Different bevacizumab products are **not interchangeable**.

Administration:

PACLitaxel

- Use non-PVC equipment, including 0.22 micron in-line filter, in order to minimize patients' exposure to DEHP leaching from PVC bags or sets; infuse over 3 hours.
- Dilute in 500-1000 mL Normal Saline or 5% Dextrose, in a final concentration of 0.3-1.2 mg/mL.
- Excessive shaking, agitation, or vibration may induce precipitation and should be avoided.
- Precipitation may rarely occur with infusions longer than 3 hours.

CISplatin

- Ensure good urinary output during chemotherapy visit. Patient should void at least once during chemotherapy visit. Use locally approved hydration regimens.
- Blood pressure should be taken before and after chemotherapy.
- Additional hydration may be ordered for hypovolemic patients.
- Hydration and diuresis for patients with pre-existing renal, cardiac, or diabetic history at discretion of physician.
- Oral hydration with 8 glasses of fluid per day is strongly encouraged on treatment day and for 1-2 days after cisplatin; if nausea and vomiting prevent oral hydration, the patient may need to return for more IV hydration.
- Cisplatin is physically incompatible with any IV set, needle or syringe containing aluminum.
- Store unopened vials between 15°C to 25°C and protect from light. Do not refrigerate or freeze since precipitation will occur.

Bevacizumab

- Bevacizumab infusions should not be administered or mixed with Dextrose or Glucose solutions due to potential for drug degradation.
- Mix in 100 mL bag NS. (Dilution should be 1.4 -16.5 mg/mL).
- Do not shake. Should not be mixed or diluted with other drugs.
- Compatible with PVC or polyolefin bags.
- DO NOT ADMINISTER AS AN IV PUSH OR BOLUS
- Infused over 90 minutes as loading dose, if tolerated next infusion can be given over 60 minutes; can thereafter be given over 30 minutes as maintenance dose
- Refrigerate unopened vials and protect from light; do not freeze.

Contraindications:

- Patients with known hypersensitivity to Chinese hamster ovary cell product, to other recombinant human or humanized antibodies, platinum-containing compounds, severe hypersensitivity reactions to paclitaxel or other drugs formulated in Cremophor EL (polyethoxylated castor oil)
- Patients with untreated CNS metastases
- Patients with recurrent hemoptysis (>2.5ml) or serious hemorrhage
- Patients with pre-existing hearing impairment, unless the possible benefits of treatment outweigh the risks.

Other Warnings/Precautions:

- Patients who have received extensive prior treatment, have poor performance status and those over 65 years of age
- Patients with a history of arterial thromboembolism or significant cardiovascular disease or cardiac failure
- Patients with coagulopathies (congenital, acquired or therapeutic)
- Hypertension should be controlled prior to starting treatment
- Bevacizumab should not be initiated for at least 28 days following major surgery or until wound healing has occurred; hold for 28 days prior to major elective surgery
- The safety and efficacy of concurrent radiotherapy and bevacizumab has not been established.
- Use with caution in patients with impaired hepatic function, including concurrent liver metastases or a previous history of hepatitis, alcoholism or liver cirrhosis
- Congestive heart failure (including LVEF decrease) has been reported in patients who have received other chemotherapy agents, especially anthracyclines.
- Paclitaxel contains ethanol, and is administered with agents such as antihistamines which cause drowsiness. Patients should be cautioned regarding driving and the use of machinery.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Recommended Clinical Monitoring

- CBC; baseline and before each cycle
- Blood pressure; baseline and every 2-3 weeks during therapy; more frequently in patients who develop hypertension
- EKG monitoring for patients with arrhythmias during previous infusions
- Dental evaluation; baseline
- Electrolytes, including magnesium, sodium, potassium, phosphate and calcium; baseline and before each cycle
- Liver and renal function tests; baseline and before each cycle
- Urine dipstick, 24 hour urine collection is recommended for patients with a 2+ or greater urine dipstick; baseline and regular
- Clinical assessment of fever, infection and bleeding, musculoskeletal, neurologic, hypersensitivity, flu-like symptoms, GI toxicity, thromboembolism; at each visit

- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

- Cardiac function tests (Echo, RNA and/or MUGA scans) especially in patients who are close to the lifetime cumulative dose of anthracyclines/anthracenediones; baseline and as clinically indicated
- Audiogram; baseline and as clinically indicated
- INR in patients receiving warfarin; baseline and regular

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J - Administrative Information

Approximate Patient Visit	7 to 8 hours
Pharmacy Workload (average time per visit)	41.424 minutes
Nursing Workload (average time per visit)	74.833 minutes

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K - References

Bevacizumab, cisplatin and paclitaxel drug monographs, Cancer Care Ontario.

Tewari KS, Sill MW, Long HJ 3rd, et al. Improved survival with bevacizumab in advanced cervical cancer. N Engl J Med. 2014 Feb 20;370(8):734-43.

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M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

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Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare

provider if they have questions regarding any information set out in the Formulary documents.

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