Regimen Monograph

A - Regimen Name

PACLTOPO+BEVA Regimen

Paclitaxel-topotecan-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) and cannot receive platinum-based chemotherapy.
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
topotecan	0.75 mg /m²	IV	Days 1 to 3
bevacizumab	15 mg /kg	IV	Day 1

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

Until disease progression or unacceptable toxicity.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate

Other Supportive Care:
Also refer to CCO Antiemetic Summary

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

• 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 treatment.

Dosage with toxicity

Hematologic toxicities

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 level	Paclitaxel (mg/m^2)	Topotecan (mg/m^2)	Bevacizumab (mg/kg)
0	175	0.75	15
-1	140	0.60	15
-2	105	0.45	15

Toxicity	Topotecan	Paclitaxel	Bevacizumab
Febrile neutropenia or Grade 4 neutropenia for > 7d	↓ 1 dose level, consider adding G-CSF for subsequent cycles if recurs*	↓ 1 dose level, consider adding G-CSF for subsequent cycles if recurs*	No change
Grade 4 thrombocytopenia or thrombocytopenic bleeding	↓ 1 dose level	↓ 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/topotecan action
Uncontrollable hypertension*			Hold*	Consider hold or discontinue
Delayed wound healing; Surgery**				
Proteinuria ≥2g/24 hours***				
Wound dehiscence; Necrotizing fasciitis			Discontinue	
Tracheo-esophageal fistula, other non-GI fistulae; GI perforation		Any internal fistula		Consider hold or discontinue
Nephrotic syndrome; non recovery of proteinuria ≥2g/24 hours	Hypertension (not controlled with medical management)	Hypertension		
Severe Hypersensitivity				
PRES/RPLS				
Arterial thromboembolism	Pulmonary embolism	Venous thromboembolism (including pulmonary embolism)		
Symptomatic cardiac failure				
Recurrent	Bleeding	Bleeding (any)		

hemoptysis > 2.5mL; Intracranial bleeding	(any)			
Any grade (continued)	**Grade 3**	**Grade 4**	**Bevacizumab action**	**Paclitaxel/topotecan action**
Grade 2 neuropathy			No change	↓ paclitaxel 2 dose levels Hold topotecan until ≤ grade 1
	Grade 3 neuropathy	Grade 4 neuropathy	No change	Hold paclitaxel and topotecan until ≤ grade 1, Resume paclitaxel at ↓ 2 dose levels. If no recovery with a 2 week hold, consider discontinuing
Grade 2 mucositis or diarrhea	Grade 3 mucositis, diarrhea or other non-hematologic toxicity		No change	Hold topotecan until ≤ grade 1, then resume at ↓ 1 dose level.
		Grade 4 mucositis, diarrhea or other non-heme toxicity	No change	Discontinue

*If held for 3 weeks, discontinue bevacizumab and continue chemotherapy. If held 4 or more weeks, discontinue treatment
**Hold for 28 days PRIOR (if surgery elective) and AFTER major surgery, or until wound healed
***May restart when < 2 g/24hrs. If held more than 2 months, discontinue bevacizumab

Hepatic Impairment

Bilirubin	Paclitaxel dose	Topotecan dose	Bevacizumab dose
1.5-2x ULN	no change	no change	no change
>2-4 x ULN	↓ 1 dose level	↓ 1 dose level	no change
> 4x ULN	discontinue	↓ 1 dose level or omit	no change

Renal Impairment

Creatinine Clearance (mL/min)	Paclitaxel dose	Topotecan dose	Bevacizumab dose
40-60	no change	no change	no change
20-39		↓ 1 dose level	
<20		discontinue	

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F - Adverse Effects

Refer to PACLitaxel, topotecan, 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
• Alopecia • Nausea, vomiting • Peripheral neuropathy (may be severe) • Musculoskeletal pain • Hypertension (may be severe) • Hypersensitivity (may be severe) • Ovarian failure • Proteinuria (may be severe) • Diarrhea (may be severe) • Constipation • Fatigue • Increased LFTs (may be severe) • Abdominal pain • Cough, dyspnea • Edema • Insomnia • Mucositis • Anorexia • Headache • Rash (may be severe)	• Arterial thromboembolism • Cardiotoxicity, arrhthymia • Pulmonary hypertension • Thrombotic microangiopathy • Fistula (GI and non-GI) • GI obstruction, perforation • Secondary malignancy • Pancreatitis • Pneumonitis • Delayed wound healing • Necrotizing fasciitis • Osteonecrosis (jaw, others) • PRES, seizure • Cystoid macular edema • Renal failure • Secondary malignancy • Encephalopathy

• Dysguesia • Myelosuppression +/- infection, bleeding (may be severe) • Hemorrhage (may be severe) • Eye disorders • Venous thromboembolism (may be severe)	

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G - Interactions

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

- Use with caution with bisphosphonates and anti-angiogenic drugs given increased risk of ONJ
- 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)
- If G-CSF is used with topotecan, give after entire topotecan dose is given
- Avoid phenytoin or monitor closely; avoid curcumin (tumeric) (these may reduce the effect of topotecan)

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H - Drug Administration and Special Precautions

Refer to PACLitaxel, topotecan, 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.

Topotecan

- Mix in 50mL-100mL minibag (NS or D5W); infuse over 30 minutes.
- Final concentration should be between 0.02 mg/mL to 0.5 mg/mL.

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, 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

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.
- 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
- Liver and renal function tests; baseline and before each cycle
- Dental evaluation; baseline
- Monitor blood pressure during paclitaxel infusion and every 2-3 weeks during bevacizumab therapy and more frequently in patients who develop hypertension.
- EKG monitoring for patients who have arrhythmia during infusion
- Baseline and regular dipstick urinalysis; 24 hour urine collection is recommended for patients with a 2+ or greater urine dipstick
- Clinical toxicity assessment (including hypersensitivity, musculoskeletal, perforation, fistula, GI symptoms, hemorrhage, infection, ONJ, thromboembolism, wound healing, hypertension, neurologic and cardiac effects); 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
- INR for patients receiving warfarin

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J - Administrative Information

Approximate Patient Visit	5.5 to 6 hours
Pharmacy Workload (average time per visit)	37.367 minutes
Nursing Workload (average time per visit)	69.833 minutes

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K - References

Paclitaxel, topotecan and bevacizumab 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.

June 2021 removed "unfunded" flag for topotecan

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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.

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Regimen Monographs

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

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