Regimen Monograph

A - Regimen Name

CRBPPGLDX Regimen

Pegylated Liposomal DOXOrubicin-CaRBOplatin

Disease Site

Gynecologic
Ovary

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

Combination treatment of platinum sensitive* recurrent ovarian, fallopian tube or primary peritoneal cancer.

Retreatment with pegylated liposomal doxorubicin (pgldx), either as a combination regimen or as a single agent, is not publicly funded. See NDFP eligibility forms for additional funding details.

*defined as a progression-free interval ≥ 6 months since the last line of platinum-based therapy

Supplementary Public Funding

pegylated liposomal DOXOrubicin
New Drug Funding Program (Liposomal Doxorubicin with Carboplatin - Platinum-Sensitive Recurrent Ovarian Fallopian Tube and Primary Peritoneal

Cancer) (NDFP Website)

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B - Drug Regimen

CARBOplatin	AUC 4 to 6	IV	Day 1

Adjust Carboplatin dose to AUC target (using Calvert formula) as outlined in "Other Notes" section. Consider dosing at the lower AUC for patients with poor performances or myelosuppressive therapy.

pegylated liposomal DOXOrubicin	30 mg /m²	IV	Day 1

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C - Cycle Frequency

REPEAT EVERY 28 DAYS

Until disease progression or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Moderate + NK1 antagonist (Carboplatin AUC ≥ 5)
Moderate (Carboplatin AUC < 5)

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

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E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

Dosage with toxicity

Dose levels are as follows:

	Starting Dose	**Dose Level -1**	**Dose Level -2**	**Dose Level -3**
Carboplatin	AUC 5	AUC 4	AUC 3	Discontinue
Pegylated liposomal doxorubicin	30 mg/m^2	25 mg/m^2	20 mg/m^2	Discontinue

Worst Toxicity in Previous Cycle	**Pegylated liposomal doxorubicin***	**Carboplatin***
Grade 2 skin/stomatitis	Delay until ≤ grade 1. If still grade 1 then ↓ by 1 Dose Level.	100%
Grade 3 skin/stomatitis	Delay until ≤ grade 1, then ↓ by 1 Dose Level. If still grade 2 or 3 then discontinue.	100%
Grade 4 skin/stomatitis	Delay until ≤ grade 1, then ↓ by 2 Dose Levels or Discontinue. If still grade 2 or 3 then discontinue.	↓ by 1 Dose Level
Grade 4 ANC ≥ 5-7 days or Grade 4 platelets, febrile neutropenia or thrombocytopenic bleeding	↓ by 1 Dose Level	↓ by 1 Dose Level
Significant cardiotoxicity	Discontinue	Discontinue
Grade 3 other toxicity	↓ by 1 Dose Level	↓ by 1 Dose Level
Grade 4 other toxicity	Discontinue	Discontinue
*Do not retreat until ANC ≥ 1.5 x 10^9/L, platelets ≥ 100 x 10^9/L and toxicity ≤ grade 2 or as detailed above		

Hepatic Impairment

	Dose modification		
Bilirubin (micromol/L)	**PGLDX**		**Carboplatin**
	Cycle 1 (% normal dose)	**Cycle 2 onwards if cycle 1 tolerated with no changes in liver function tests (% normal dose)**	**Each cycle**
21-51	75%	100%	No adjustment
>51	50%	75%*	No adjustment

* The dosage can be increased for subsequent cycles if tolerated.

Renal Impairment

Creatinine Clearance (ml/min)	Dose modification	
	PGLDX	**Carboplatin**
30 - 50	No adjustment	Use Calvert formula*
20-30	No data available. Use with extreme caution	Use Calvert formula*
< 20	No data available. Use with extreme caution	Discontinue

* See Other Notes- Appendix for Calvert formula

Dosage in the Elderly

Caution should be exercised and dose reduction considered for carboplatin as elderly patients may have more severe myelosuppression and neuropathy.

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F - Adverse Effects

Refer to pegylated liposomal DOXOrubicin, CARBOplatin drug monograph(s) for additional details of adverse effects

Very common (≥ 50%)	Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Myelosuppression +/- infection, • bleeding (may be severe) • Nausea, vomiting	• Hand-foot syndrome • Increased LFTs • Nephrotoxicity	• Mucositis • Alopecia • Fatigue • Anorexia • Rash (may be severe) • Electrolyte abnormalities • Nephrotoxicity (may be severe) • Ototoxicity	• Peripheral neuropathy • Arterial / venous thromboembolism • Cardiotoxicity • Arrhythmia • Hemolytic uremic syndrome • Hypersensitivity • Secondary malignancies

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G - Interactions

Refer to pegylated liposomal DOXOrubicin, CARBOplatin drug monograph(s) for additional details

- Avoid calcium channel blockers given increased risk of cardiotoxicity
- Avoid protease inhibitors (e.g. zidovudine) as pgldx may decrease its effect
- Caution and monitor in patients with prior radiation as pgldx is a radiation sensitizer
- Avoid pgldx for up to 24 weeks after stopping trastuzumab given increased risk of cardiotoxicity
- Caution and monitor drug levels with phenytoin
- Caution and monitor INR with warfarin

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H - Drug Administration and Special Precautions

Refer to pegylated liposomal DOXOrubicin, CARBOplatin drug monograph(s) for additional details

Administration:

Pegylated liposomal doxorubicin

- Pegylated liposomal doxorubicin must not be given by the intramuscular or subcutaneous route.
- For dose < 90mg, dilute drug in 250mL D5W.
- For dose ≥ 90mg, dilute drug in 500mL D5W.
- Only use 5% Dextrose solution for further dilution. Use of other diluents or ones containing bacteriostatic agents (i.e. benzyl alcohol) may cause drug precipitation.
- Do not administer as a bolus injection or undiluted solution. The Caelyx® infusion line can be connected through the side port of a 5% Dextrose infusion for further diluent, or to minimize risk of thrombosis or extravasation.
- Do not use in-line filters. Do not admix Caelyx® with other drugs.
- To minimize the risk of infusion reactions, the initial dose is administered at a rate no greater than 1 mg/minute. If no infusion reaction is observed, subsequent infusions may be administered over 60-minutes (in ovarian or breast cancer) and 30 minutes (for Kaposi's sarcoma patients).
- The following graduated rate was used for patients who experienced an infusion reaction in the breast clinical trial: 5% of the total dose infused IV over 15 minutes. If tolerated, double the infusion rate for the next 15 minutes. If tolerated, complete the infusion over the next hour for a total infusion time of 90 minutes.
- Avoid extravasation. It may occur with or without an accompanying stinging or burning sensation, and even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation occur, the injection or infusion should be immediately terminated and restarted in another vein. Any known or suspected extravasation should be managed promptly.

Carboplatin

- Mix in 100mL to 250mL bag (5% Dextrose or Normal Saline); infuse IV over 15 to 60 minutes.
- Incompatible with sets, needles or syringes containing aluminum – leads to precipitation and loss of potency.
- Protect from light.

Contraindications:

- Patients who have a hypersensitivity to these drugs or other platinum-containing compounds, doxorubicin, other anthracyclines or anthracenediones
- Patients with severe renal impairment, severe myelosuppression or bleeding tumours

Warnings / precautions:

- Patients with a history of cardiovascular disease and/or prior anthracycline use
- Patients with abnormal renal function or who are receiving concomitant nephrotoxic drugs
- Patients who have received extensive prior treatment, have poor performance status and those over 65 years of age
- Use pgldx with caution in patients with diabetes as the infusate is dextrose water
- Do not use pgldx interchangeably with other formulations of doxorubicin

Pregnancy and lactation:

- This regimen is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least 6 months after the last dose.
- Breastfeeding is not recommended.

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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

- Liver and renal function tests and electrolytes; baseline and before each cycle
- CBC; baseline and before each cycle
- Cardiac function tests (Echo, RNA and/or MUGA scans) for all patients with cardiac risk factors and before each additional dose over the cumulative dose threshold of 450mg/m^2 (Cumulative dose lower for high risk patients); baseline and as clinically indicated
- Clinical assessment of GI toxicity, rash, hypersensitivity, hand-foot syndrome, infection, bleeding, cardiac toxicity, neurotoxicity and ototoxicity; at each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

INR; Baseline and as clinically indicated

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J - Administrative Information

Approximate Patient Visit	2 hours
Pharmacy Workload (average time per visit)	26.091 minutes
Nursing Workload (average time per visit)	49.167 minutes

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K - References

Markman M, Moon J, Wilczynski S, et al. Single agent carboplatin versus carboplatin plus pegylated liposomal doxorubicin in recurrent ovarian cancer: Final survival results of a SWOG (S0200) phase 3 randomized trial. Gynecol Oncol 2010;116(3):323-5.

Pignata S, Scambia G, Ferrandina G, et al. Carboplatin plus paclitaxel versus carboplatin plus pegylated liposomal doxorubicin as first-line treatment for patients with ovarian cancer: the MITO-2 randomized phase III trial. J Clin Oncol 2011;29(27):3628-35.

Pujade-Lauraine E, Wagner U, et al. Pegylated liposomal doxorubicin and carboplatin compared with paclitaxel and carboplatin for patients with platinum-sensitive ovarian cancer in late relapse. J Clin Oncol. 2010;28 (20):3323-9.

Wagner U, Marth C, Largillier R, et al. Final overall survival results of phase III GCIG CALYPSO trial of pegylated liposomal doxorubicin and carboplatin vs paclitaxel and carboplatin in platinum-sensitive ovarian cancer patients. Br J Cancer 2012;107(4):588-91.

Carboplatin and pegylated liposomal doxorubicin drug monographs, Cancer Care Ontario.

PEBC Advice Documents or Guidelines

- Systemic Therapy for Recurrent Epithelial Ovarian Cancer

June 2022 Re-linked NDFP form; Modified Dosage in renal impairment and Other notes sections

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L - Other Notes

Calvert Formula

DOSE (mg) = target AUC X (GFR + 25)

- AUC = product of serum concentration (mg/mL) and time (min)
- GFR (glomerular filtration rate) expressed as measured Creatinine Clearance or estimated from Serum Creatinine (by Cockcroft and Gault method or Jelliffe method)

(Calvert AH, Newell DR, Gumbrell LA, et al, Carboplatin dosage: Prospective evaluation of a simple formula based on renal function. J Clin Oncol, 1989; 7: 1748-1756)

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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.

The format and content of the drug monographs, regimen monographs, appendices and symptom management

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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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