Regimen Monograph

A - Regimen Name

PGLDX Regimen

Pegylated Liposomal DOXOrubicin

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

- Treatment of platinum-sensitive recurrent ovarian cancer, when platinum is contraindicated (e.g. due to toxicity)
- Treatment of platinum-resistant recurrent ovarian cancer

Supplementary Public Funding

pegylated liposomal DOXOrubicin
New Drug Funding Program (Liposomal DOXOrubicin - Single Agent Treatment of Platinum Sensitive Ovarian Fallopian Tube or Primary Peritoneal Cancer) (NDFP Website)

pegylated liposomal DOXOrubicin
New Drug Funding Program (Liposomal Doxorubicin - Platinum-Resistant Ovarian Fallopian Tube or Primary Peritoneal Cancer) (NDFP Website)

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B - Drug Regimen

pegylated liposomal DOXOrubicin	40 - 50 mg /m²	IV	Day 1

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C - Cycle Frequency

REPEAT EVERY 28 DAYS

Until evidence of stable disease, metastatic progression, or unacceptable toxicity

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D - Premedication and Supportive Measures

Antiemetic Regimen: Low

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

Worst Toxicity & Toxicity on day of planned dosing	Action*: Week 4-5	Action*: Week 6
Grade 1 skin/stomatitis	If was ≥ grade 3, delay for 1-2 weeks; otherwise treat on time	If still grade 1, ↓ dose by 25%
Worst Toxicity & Toxicity	**Action*: Week 4-5**	**Action*: Week 6**

on day of planned dosing		
Grade 2 skin/stomatitis	Delay for 1-2 weeks;	If still grade 1 or 2, ↓ dose by 25%
Grade 3 or 4 skin/stomatitis	Delay for 1-2 weeks;	Discontinue if still ≥ grade 3 Consider discontinuing if was grade 4 Otherwise ↓ dose by 25%
Grade 4 ANC, platelets, febrile neutropenia or thrombocytopenic bleeding	↓ dose by 25%	
Significant cardiotoxicity	Discontinue	
Grade 3 other	↓ dose by 25%	
Grade 4 other	Discontinue	
*Do not retreat until ANC > 1.5 x 10^9/L, platelets > 75-100 x 10^9/L and other toxicity ≤ grade 2 / or as indicated above		

Management of Infusion-related reactions with Anthracyclines:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms.	• Consider pre-medications and administering at a slower infusion rate.
3 or 4	• Stop treatment. • Aggressively manage symptoms.	• Re-challenge is discouraged, especially if vital signs have been affected. • Consider desensitization if therapy is necessary.

Hepatic Impairment

Bilirubin (µmol/L)	Cycle 1 (% standard dose)	Cycle 2 onwards if cycle 1 tolerated with no changes in liver function tests (% standard dose)
21-51	75%	100%
>51	50%	75%*

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

Renal Impairment

No modifications are necessary for mild to moderate renal impairment (creatinine clearance > 30 mL/min). No studies have been done in patients with severe renal impairment.

Dosage in the Elderly

Limited information in patients ≥ 60 years. Use with caution.

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F - Adverse Effects

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

Most Common Side Effects	Less Common Side Effects, but may be Severe or Life-Threatening
• Myelosuppression ± infection/bleeding (may be severe) • Palmar-plantar erythrodysesthesia (Hand-foot syndrome) • Stomatitis • Fatigue • Acute Hypersensitivity reactions (first infusion) • Nausea and vomiting • Rash (may be severe) • Alopecia • Anorexia	• Arterial, venous thromboembolism • Secondary malignancy • Cardiac toxicity • Phlebitis

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G - Interactions

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

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H - Drug Administration and Special Precautions

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

Administration:

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 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.
- 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.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Contraindications:

- patients who have a history of hypersensitivity reactions to a conventional formulation of doxorubicin, other anthracyclines, anthracenediones, or components of the pegylated liposome

Other Warnings/ Precautions:

- use with caution in patients with a history of cardiovascular disease and/or prior anthracycline use
- care should be exercised in patients with diabetes as the infusate is dextrose water

- pegylated liposomal doxorubicin (Caelyx) is a unique formulation of doxorubicin and should never be used interchangeably with other formulations of doxorubicin

Pregnancy and Lactation:

- Pegylated liposomal doxorubicin 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.
- Pegylated liposomal doxorubicin is contraindicated in breastfeeding.

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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

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

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J - Administrative Information

Approximate Patient Visit	1 hour
Pharmacy Workload (average time per visit)	19.371 minutes
Nursing Workload (average time per visit)	39.167 minutes

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K - References

Pegylated liposomal doxorubicin drug monograph, Cancer Care Ontario.

Ferrandina G, Ludovisi M, Lorusso D, et al. Phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in progressive or recurrent ovarian cancer. J Clin Oncol 2008;26(6):890-6.

Gordon AN, Tonda M, Sun S, et al. Long-term survival advantage for women treated with pegylated liposomal doxorubicin compared with topotecan in a phase 3 randomized study of recurrent and refractory epithelial ovarian cancer. Gynecol Oncol 2004;95(1):1-8.

Gordon A, Fleagle J Guthrie D et al. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. J Clin Oncol 2001;19(14):3312-22.

Mutch DG, Orlando M, Goss T, et al. Randomized phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer. J Clin Oncol.2007;25(19):2811-8.

PEBC Advice Documents or Guidelines

- Systemic Therapy for Recurrent Epithelial Ovarian Cancer

December 2019 Updated infusion reaction information in Dose Modification section

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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 information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

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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