BC CANCER
Provincial Health Services Authority

Pharmacy FAQ

Lifetime Cumulative Dose Documentation for Anthracyclines and Bleomycin

1. Why should we document cumulative doses of anthracyclines?

Anthracyclines, which include **daunorubicin**, **doxorubicin** (including pegylated liposomal), **epirubicin**, **idarubicin** and the anthracenedione **mitoxantrone**, can increase the risk of potentially irreversible cardiac toxicity. This is thought to be caused by mechanisms such as damage to the myocardial tissue by highly reactive free radicals. Cardiotoxicity may manifest as acute (transient) or delayed (progressive). Progressive cardiotoxic effects are dose-related with risk increasing steeply at higher cumulative doses. These effects may present as decreased left ventricular ejection fraction (LVEF) or even symptomatic congestive heart failure (CHF) years after treatment is completed. Since progressive anthracycline-induced cardiotoxicity is related to the total cumulative dose, it is important to monitor a patient's lifetime doses of anthracyclines.[1-7]

Anthracycline drug manufacturers have suggested *maximum lifetime cumulative dose* limits beyond which the risk of cardiotoxicity was seen to substantially increase. Patients should undergo pretreatment assessment and monitoring should start once they approach the monitoring threshold, or at a lower threshold if the patient has pre-existing cardiac or other risk factors. Cancer treatment related risk factors include previous or concurrent therapy with other cardiotoxic drugs such as trastuzumab, cyclophosphamide, and mitomycin, or with high dose mediastinal irradiation to the heart. Other cardiac risk factors include increased age, family history, obesity, diabetes, smoking, hypertension, or preexisting cardiac dysfunction. As patients approach their suggested maximum lifetime cumulative dose, the risk vs. benefit of ongoing treatment must carefully be considered, and further cardiac assessment may be warranted.[1-7]

The doxorubicin monograph in the Cancer Drug Manual contains information on anthracycline cardiotoxicity, monitoring thresholds, conversion factors and management. Pharmacists may be asked to convert cumulative dose from one anthracycline to another. The table below provides a guide for the cumulative dose thresholds at which to start cardiac monitoring in adults with normal cardiac function at baseline. **Lower monitoring thresholds may be used for patients with additional cardiac risk factors**. Note that individual patient sensitivity to anthracycline-induced cardiac toxicity varies, and patients may tolerate lower or higher cumulative doses.

Table 1: Recommended Anthracycline Conversion Factors & Lifetime Cumulative Dose Monitoring Thresholds for Adults*

Drug	Conversion Factor** to Doxorubicin dose [1]	Suggested Monitoring Threshold [1]	Comments [1]
DAUNOrubicin	x 0.5 - 0.83	450 mg/m²	Suggested lifetime limit: 900 mg/m^2 or 25 mg/kg [8]
DAUNOrubicin in DAUNOrubicin-cytarabine liposome (VYXEOS®)	Same as conventional DAUNOrubicin	Same as conventional DAUNOrubicin	VYXEOS monograph suggests lifetime limit of 550 mg/m^2 (400 mg/m2 in patients who received mediastinal irradiation) [9]
DOXOrubicin	x 1	300 mg/m²	Suggested lifetime limit: 550 mg/m^2 (3 week cycle), 700 mg/m^2 (1 week cycle) If risk factors are present: 400-450 mg/m^2 (3 week cycle), 550 mg/m^2 (1 week cycle)
DOXOrubicin, Pegylated Liposomal	Unknown	Unclear relationship between cumulative dose and cardiotoxicity. 400-450 mg/m^2 [10]	No lifetime limit identified. Cardiac toxicity seen at doses above and below 550 mg/m^2, although less common than with conventional doxorubicin. More common in patients with previous anthracycline exposure, mediastinal radiation, or other cardiac risk factors. Doses exceeding 2000 mg/m^2 tolerated in some patients. Routine baseline and ongoing LVEF assessment have been suggested. [11,12]
Epirubicin	x 0.5 - 0.67	600 mg/m²	Suggested lifetime limit: 720-1000 mg/m^2 Risk increases more steeply above 900 mg/m^2 [13]
IDArubicin	x 2 – 5	150 mg/m²	No lifetime limit identified. IV doses: Cardiomyopathy was reported in 5% of patients who received cumulative IV doses of 150-290 mg/m^2. PO doses: Cumulative PO doses up to 400mg/m^2 had low probability of cardiotoxicity. [14]
MitoXANTRONE	x 2.2 – 4	100 [15] -140 mg/m²	Suggested lifetime limit: 160 mg/m^2

*Lower monitoring thresholds and maximum cumulative doses may be used for patients with cardiac risk factors

**CST Cerner electronic health record uses high limit of conversion factor range when converting to doxorubicin equivalent dose (e.g., 0.67 for epirubicin)

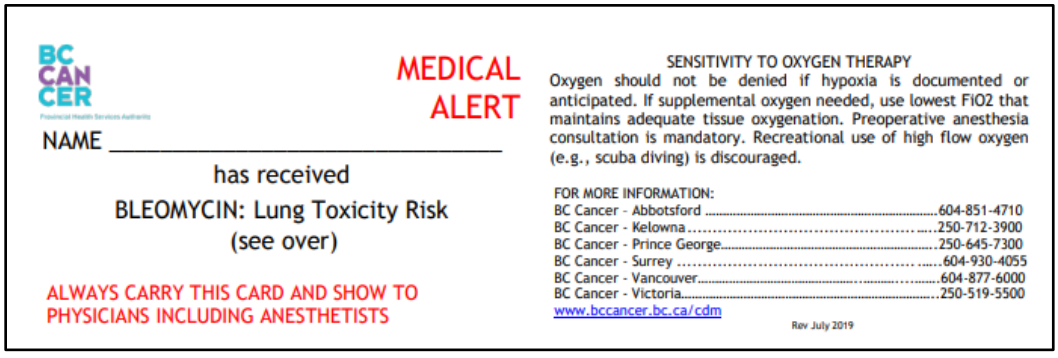
2. Why should we document cumulative doses of bleomycin?

Bleomycin is another agent for which pharmacists keep a record of cumulative doses. The most serious side effects of bleomycin are respiratory and can occur in 10% of patients. Bleomycin pulmonary toxicity (BPT) can progress to pneumonia, pulmonary fibrosis and death in 1% of patients. Identification of patients with BPT can be very difficult due to the nonspecific signs and symptoms, which can progress subtly and rapidly. Non-specific symptoms include dyspnea, dry cough, basal rales, pleuritic chest pain and fever. Patients may have reduced lung capacities in pulmonary function tests. Risk factors for developing BPT include age over 40 years, compromised pulmonary or renal function, concomitant chest irradiation, concomitant therapy with other cancer drugs (eg., cisplatin, gemcitabine, cyclophosphamide, methotrexate, etc.), smoking history, and a high cumulative dose of bleomycin. [1,16-18]

It is important to maintain a record of the lifetime doses of bleomycin that a patient receives. Pulmonary toxicity is more common in patients over 70 years and risk increases steeply at total doses greater than **400 units** (less for patients with renal or pulmonary impairment).[1,17] BPT can occur at lower doses when given in combination with other chemotherapy drugs, and BC Cancer protocols such as GOBEP suggest limiting bleomycin total dose to **270 units**. Bleomycin doses given via intraperitoneal or intrapleural route should be counted as half doses due to their lower systemic absorption. Intravesical doses are considered minimally absorbed. [1,16]

Oxygen therapy may also precipitate or aggravate bleomycin pulmonary toxicity, causing lung injury to occur at lower oxygen concentrations than normal.[1,16-18] The bleomycin monograph describes respiratory effects, management and recommendations for oxygen therapy after treatment, for example when it used in surgical anesthesia. At BC Cancer, patients are given a Medical Alert card to inform other health care providers of lung toxicity risk and sensitivity to oxygen therapy. See below.

Figure 1. Bleomycin alert card


BC CANCER

MEDICAL ALERT

NAME _____

has received

BLEOMYCIN: Lung Toxicity Risk

(see over)

ALWAYS CARRY THIS CARD AND SHOW TO PHYSICIANS INCLUDING ANESTHETISTS

SENSITIVITY TO OXYGEN THERAPY

Oxygen should not be denied if hypoxia is documented or anticipated. If supplemental oxygen needed, use lowest FiO2 that maintains adequate tissue oxygenation. Preoperative anesthesia consultation is mandatory. Recreational use of high flow oxygen (e.g., scuba diving) is discouraged.

FOR MORE INFORMATION:

BC Cancer - Abbotsford 604-851-4710
BC Cancer - Kelowna 250-712-3900
BC Cancer - Prince George.....250-645-7300
BC Cancer - Surrey 604-930-4055
BC Cancer - Vancouver.....604-877-6000
BC Cancer - Victoria.....250-519-5500

www.bccancer.bc.ca/cdm

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3. How to document cumulative doses of anthracylines and bleomycin?

A cumulative dose record for all anthracyclines and bleomycin is kept either electronically (for sites using an electronic health record), or on a paper record located in the physical patient chart.

The dose of anthracycline is added at each cycle. When the patient is getting close to the monitoring threshold (e.g., 300 mg/m² for doxorubicin) the physician should be alerted, unless it is the patient's last cycle. The use of alternative anthracyclines, such as epirubicin or liposomal doxorubicin, or a change in administration frequency from every 3 weeks to a lower weekly dose, can reduce the risk of cardiotoxicity.[1,6] For patients who have reached a cumulative dose of 300 mg/m² doxorubicin equivalent, therapy with the cardio-protective agent dexrazoxane can be considered.[1,5] [For more information on dexrazoxane, please refer to the Dexrazoxane FAQ].

The cumulative dose of bleomycin units is similarly added.

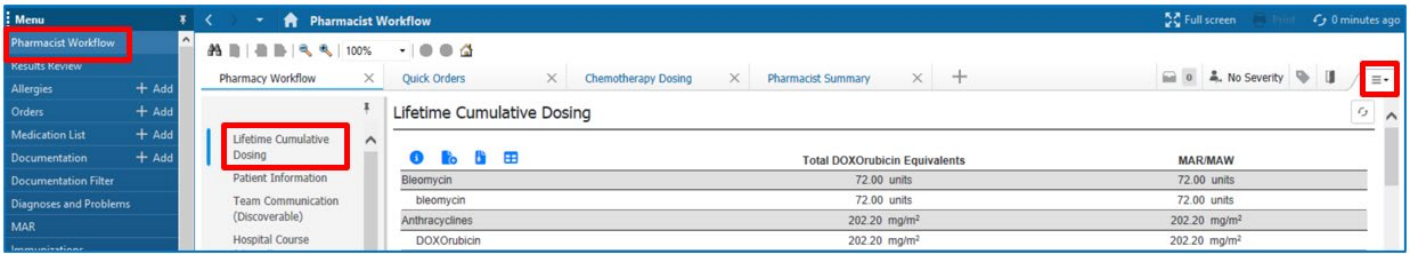
See below for examples of documentation of doses for **adult** patients. Pediatric doses are recorded separately, for example on a separate Pediatric Lifetime Cumulative Dosing PowerForm in the CST Cerner electronic health record.

Electronic Record

Sites using CST Cerner view an adult **Lifetime Cumulative Dosing component** that can be accessed from the patient chart via an appropriate workflow page [e.g., ONC/HEM/BMT Workflow (Nursing), Outpatient Chart (Provider), Pharmacist Workflow (Pharmacy, see Figure 2)]. Pegylated liposomal doxorubicin doses are not documented here as there is no conversion factor to calculate doxorubicin equivalent doses.

- Any anthracycline or bleomycin doses given at sites using CST Cerner electronic Medication Administration Record (eMAR) for oncology drugs as of Aug 28, 2024 **automatically** flow into the Lifetime Cumulative Dosing component. This occurs via the Medication Administration Record/Medication Administration Wizard (MAR/MAW), once the nurse signs medication administration in the eMAR.

Figure 2. Accessing Lifetime Cumulative Dosing component in Pharmacist Workflow*
(site using CST Cerner eMAR for oncology drugs)



*At first time use, the component may have to be added to the Workflow page by clicking on ☰▾ and selecting Lifetime Cumulative Dosing from the list of Components.

- Any anthracycline or bleomycin doses given outside of CST Cerner eMAR (External/Historical/CST Site Paper MAR dose administrations) require **manual entry** using the **Lifetime Cumulative Dosing External Administrations PowerForm** (Figure 3) to be included in the Lifetime Cumulative Dosing component (Figure 4).

Figure 3: Lifetime Cumulative Dosing External Administrations PowerForm

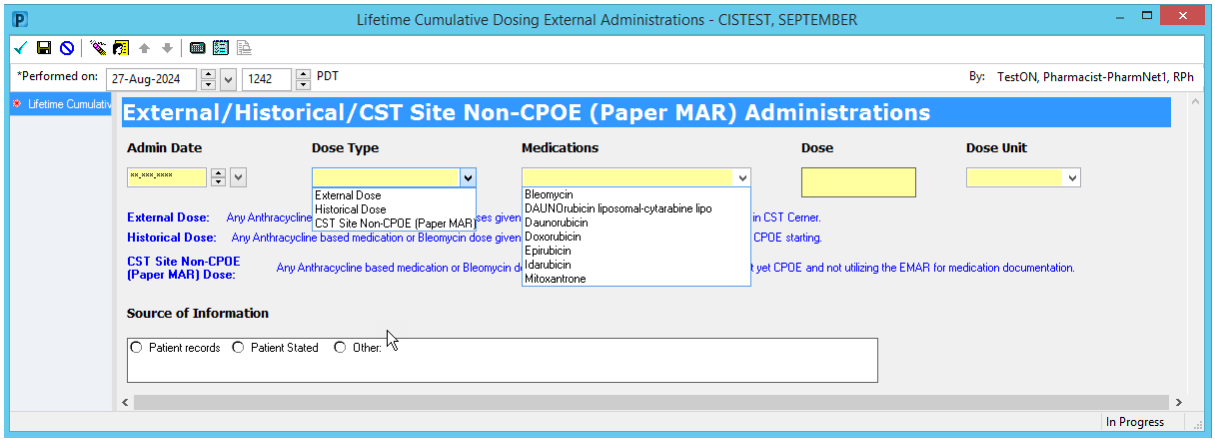
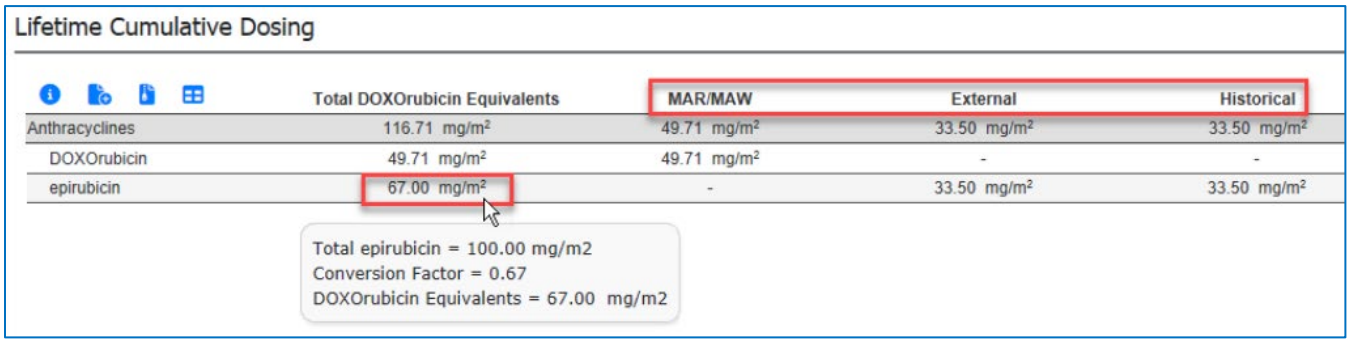


Figure 4. Sample Lifetime Cumulative Dosing component display



The adult **Lifetime Cumulative Dosing (LCD) component** converts anthracycline doses to doxorubicin equivalent doses. Using the epirubicin in Figure 4 as an example, External and Historical doses of epirubicin were manually recorded using the LCD External Administrations PowerForm. Those entries then flowed to the LCD component and displayed as 67 mg/m^2 doxorubicin equivalent dose (total epirubicin dose 100 mg/m^2), resulting in a total doxorubicin equivalent dose of 116.71 mg/m^2 to date for this patient. When this patient nears the monitoring threshold (e.g., 300 mg/m^2 doxorubicin equivalents) the physician should be alerted, unless it is the patient's last cycle. Note that the CST Cerner electronic health record used the larger 0.67 epirubicin conversion factor resulting in a larger estimate of doxorubicin equivalent dose 67 mg/m^2 (more conservative). Using the smaller conversion factor 0.5 from the range of recommended conversion factors would only have converted into 50 mg/m^2 doxorubicin equivalents.

Paper Record

The dose of anthracycline is added at each cycle and the cumulative dose/m² is manually calculated based on the most recent BSA (Figure 5). The cumulative dose of pegylated liposomal doxorubicin may also be recorded although the relationship between cumulative dose and cardiotoxicity is unclear. Similarly, cumulative dose units of bleomycin are manually calculated (Figure 6).

See examples of paper lifetime cumulative dose records below.

Figure 5 Sample paper record for manual recording of cumulative anthracycline doses

Anthracycline Lifetime Cumulative Dose Monitoring

Anthracycline: _____

Date	Prescribed Dose (mg/m^2)	Lifetime Cumulative Dose in (mg/m^2)

Figure 6 Sample paper record for manual recording of cumulative bleomycin doses

Bleomycin Lifetime Cumulative Dose Monitoring

Date	Prescribed Dose (units)	Lifetime Cumulative Dose (units)

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