Oncology Pharmacy Newsletter

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The Oncology Pharmacy Newsletter is publication dedicated to providing useful information for the staff treating patients who come to the Oncology Outpatient Pavilion.

We welcome questions and requests for topics.

References available upon request.

Are consents needed for Rituximab and Cyclophosphamide for non-Oncology uses?

At this time, the only patients we formally consent using our form are the Oncology patients.

Remember that consents are good for 6 months from the date of signing. Patients must be re-consented every 6 months or when a new chemotherapy or biologic medication is added to their Oncology regimen.

Anthracyline Induced Cardiotoxicity

Which drugs are anthracyclines?

The anthracycline group of chemotherapeutic agents includes doxorubicin, idarubicin, daunorubicin, epirubicin, and mitoxantrone. All of these agents are associated with varying degrees of cardiotoxicity, particularly in higher doses or in individuals with risk factors.

What are the symptoms?

Anthracyclines are known to cause arrhythmias, cardiomyopathy leading to heart failure, and angina or myocardial infarctions due to vasoocclusion or spasm. Symptoms include chest pain, irregular heartbeat, shortness of breath, swelling of extremities, difficulty with exertion.

When does it occur?

Acute toxicity such as atrial fibrillation or pericarditis-myocarditis can occur and often resolve within a week of discontinuing therapy. Chronic toxicity such as cardiomyopathy is more common, dose limiting, often occurs after completion of treatment, and can be permanent. It may also occur many years after the last dose of anthracycline, as in adult survivors of a childhood malignancy. Most regimens recommend repeat cardiac screening at 300mg/m2 cumulative dose of doxorubicin, or a similarly toxic amount of a different anthracycline as evaluated in “doxorubicin isotoxic equivalents”.

How does it happen?

Myocardial necrosis occurs following exposure to anthracycline leading to cardiac myopathy. It is thought to be the result of the anthracycline’s interaction with topoisomerase – II beta, which leads to cell death. Eventually enough exposure can lead to symptomatic heart failure.

Who is at risk?

Patients with preexisting heart disease, hypertension, advanced age, high cumulative doses of anthracycline, or other concurrent cardiotoxins are at increased risk. Long survival after receiving anthracyclines also increases the risk of cardiac toxicity. Children are at increased risk for cardiotoxicity, and tolerate lower cumulative doses. Radiation to the mediastinal area, previous or concurrent, also increases risk. Co-administration of cardiotoxic antitumor agents, such as taxanes, pertuzumab or trastuzumab, is thought to increase the risk of cardiotoxicity.

How do we reduce their risk?

The most common approach to reducing cardiac toxicity is monitoring total dose to avoid exceeding the cardiotoxic threshold for a given agent. While most patients will not experience cardiotoxicity below this threshold cumulative dose, some will, so it is important to monitor patients for symptoms of cardiotoxicity at each visit. Patients should have baseline cardiac screening performed and this screening should be repeated at predetermined intervals and if symptoms appear.

Administering a lipid encapsulated formulation such as liposomal doxorubicin or daunorubicin has been shown to reduce cardiotoxicity. However, at this time, lipid formulations are not generally first line, curative therapies.

Adding a protective agent such as dexrazoxane with doxorubicin or epirubicin has been shown to reduce cardiotoxicity, however, there are currently concerns over the possibility of reduced response to chemotherapy when dexrazoxane is used. Dexrazoxane is generally used in the metastatic setting in patients who have already received more than 300mg/m2 doxorubicin. These patients should have continued monitoring for cardiac adverse effects.

Modifying the doxorubicin's structure has led to the development of epirubicin and mitoxantrone. Both of these agents are less cardiotoxic, but not free from adverse cardiac effects.

Prolonged infusions may improve cardiac toxicity profile, but are not generally used due to need for hospitalization to administer anthracyclines in this fashion. Although EPOCH regimens have been given as outpatient continuous infusions, the doxorubicin dose used in this regimen is a lower dose than many other regimens (10mg/m2 x6 cycles).

It is not yet known whether agents such as beta blockers (metoprolol or carvedilol), ACE inhibitors (Lisinopril), or ARBS (valsartan) are cardioprotective when used with anthracycline therapy.

What monitoring is required?

Although specific guidelines are not established, many recommendations can be found. Baseline physical exam, ECG, MUGA to determine LVEF, and management of preexisting hypertension and/or hyperlipidemia should be performed. These should be repeated when doses of 300mg/m2 doxorubicin isotoxic equivalents are reached or when patient is symptomatic. Continued monitoring is often recommended 3, 6, and 12 months after completion of therapy, and whenever clinical symptoms dictate.

Can "maximum cumulative doses" be exceeded?

In some patients, there may be an indication to exceed the "maximum cumulative dose" of a given anthracycline. The Oncologist may at times prescribe higher doses to patients expected to see a clinical benefit from more anthracycline, and who are not exhibiting symptoms of cardiac toxicity or evidence of cardiac damage on repeated testing. These patients should receive frequent cardiac reevaluations during therapy.

What about trastuzumab, ado-trastuzumab, and pertuzumab?

Trastuzumab has been shown to decrease left ventricular ejection fraction, and, less commonly, to cause heart failure. For this reason, it is not generally given concurrently with anthracyclines such as doxorubicin. Older patients (>50) and those with preexisting anthracycline exposure, preexisting decrease in LVEF, obesity, or taking antihypertensive agents are at greater risk.

Trastuzumab cardiotoxicity is generally reversible. Baseline monitoring of cardiac function is recommended for patients in both the adjuvant and metastatic setting. Repeat assessment should be performed on patients with symptoms. Routine reassessment recommendations vary in stringency and are dependent on the patient's risk factors and intent of treatment, but NCCN suggests assessment of LVEF at 3, 6, and 9 months following baseline screening for a 1 year course of trastuzumab. Other recommendations suggest monitoring at baseline, 3, 6, 9, 12 and 18 months.

Some patients may tolerate a re-challenge of trastuzumab once the original cardiac effects have resolved.

There can be significant cardiotoxicity associated with taxane use, but concurrent use of a taxane with trastuzumab does not increase the risk of cardiotoxicity. Concurrent radiation also does not increase risk of trastuzumab induced cardiotoxicity.

At this point, ado-trastuzumab and pertuzumab appear to be less cardiotoxic than trastuzumab. Due to concerns of additive cardiotoxicity, trastuzumab, ado-trastuzumab and pertuzumab are not to be used concurrently with anthracyclines.

Although ado-trastuzumab has not been shown to cause a significant impact on LVEF, routine monitoring of LVEF is recommended by the FDA at baseline and every 3 months during treatment.

Unless symptomatic, cardiac function testing is rarely performed in patients with metastatic disease receiving these agents.

What other chemotherapeutic agents are associated with cardiac toxicities?

Other cardiotoxic chemotherapeutic agents include: Cyclophosphamide, ifosfamide, docetaxel, paclitaxel, capecitabine, and fluorouracil.

References:

http://www.uptodate.com/contents/cardiotoxicity-of-anthracycline-like-chemotherapy-agents?source=machineLearning&search=anthracycline+cardiotoxicity&selectedTitle=1%7E150&sectionRank=2&anchor=H16385821#H16385821

http://www.uptodate.com/contents/cardiotoxicity-of-trastuzumab-and-other-her2-targeted-agents?source=search_result&search=anthracycline+cardiotoxicity&selectedTitle=2%7E150

http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

R Berardi et al, Critical Reviews in Oncology/ Hematology 88 92013) 75-86

Additional references available upon request.

Suggestions for topics, questions, and comments are welcome! Just reply to sender of this newsletter or email:

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From our Billing Desks:

Please clearly distinguish between Emend Tripaks brought in by a patient, and ones dispensed by UConn Health Pharmacy, but from which we administer the first dose, when documenting on the MAR.

The patient supplied medication should read, "Patient's own med".

UConn Health supplied medication should read, "Administered 125mg from Emend Tripak from UConn Health", to avoid billing confusion. ~ *Thank you !*

Standard Volume Rituximab Infusions

Due to changes in available Pharmacy technology, all rituximab infusions will eventually be mixed to a total volume of 500ml NS. Many institutions already administer rituximab in this fashion.

Rituximab must be diluted to a final concentration of 1-4mg/ml before infusion, and the final volume of 500ml will accomplish this for the vast majority of doses administered here. For those few patients that we administer doses under 500mg, Pharmacy will mix the rituximab in an appropriately reduced final volume to maintain this concentration.

There is a rate calculator being developed that will allow the administering nurse to enter the specific dose and print out a titration sheet that provides the infusion rate for each increase based on a starting rate of 25mg/ hour, 50 mg/hour or 100mg/hour. This calculator will located on the Pharmacy Webpage and will be similar to the IVIG calculator already in use.

ANTHRACYCLINE LIFETIME CUMULATIVE DOSE Pt Name:_____

T0_____ DOB:____/____/_____

Anthracyclines may cause cardiotoxicity. Increased incidence and severity are associated with higher lifetime exposure. Current recommendations suggest limiting lifetime exposure to 450-500mg/m2 of Doxorubicin isotoxic equivalents. At the MD's discretion, this dose can be exceeded if recent cardiac evaluation is good. The following conversion factors are an estimate only. Liposomal products convey a significantly lower risk of cardiotoxicity, but are currently evaluated as the active chemical. Cumulative maximum doses have not been established for liposomal preparations.

Doxorubicin x 1 Daunorubicin x 0.833 Epirubicin x 0.67 Idarubicin x 5 Mitoxantrone x 4

Previous Anthracycline drug/total dose:_____

Baseline Cardiac testing preformed:_____

Other Risk Factors: [ ] Trastuzumab [ ]Pertuzumab [ ]Ado-trastuzumab [ ]Other_____

Date	**Drug**	**Dose in mg/m2**	**Factor**	**Equivalent**	**Cumulative dose**