Systemic Therapy Update

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EDITOR'S CHOICE

2011-2012 NEW DRUG PROGRAMS

The **Provincial Systemic Therapy Program** has approved funding for five new treatment programs based on reviews and recommendations by the BCCA's Priorities and Evaluation Committee (PEC).

Gastrointestinal:

- **Oxaliplatin with Fluorouracil/Leucovorin and Irinotecan as First-Line Palliative Treatment of Metastatic Pancreatic Cancer (UGIFIRINOX)** – In a phase III trial, FOLFIRINOX was associated with significant improvement in overall survival compared to weekly gemcitabine, which is the current standard of care at the BCCA (11.1 mo vs. 6.8 mo, respectively). Because grade 3/4 adverse event rate was also higher with FOLFIRINOX, careful selection of appropriate patients as outlined in the chemotherapy protocol is warranted. (*NEJM* 2011;364:1817-1825)

  Everolimus or SUNItinib as Palliative Treatment of Advanced Pancreatic Neuroendocrine Tumours (PNETs) (UGIPNEVER, UGIPNSUNI) – Both agents have shown significant improvement in progression free survival in patients with unresectable, well-to-moderately differentiated PNETs compared to placebo in phase III trials (everolimus: 11 mo vs. 4.6 mo [HR 0.35, p<0.0001]; SUNItinib: 11.4 mo vs. 5.5 mo [HR 0.42, p=0.0001]). (*NEJM* 2011;364:514; *NEJM* 2011;364:501)

SUNItinib demonstrated an overall survival benefit at 6 months (85.2% vs. 92.6% [p=0.02]), while everolimus did not after a follow-up of more than 2 years. The benefit of sequential therapy with everolimus and SUNItinib is not established, therefore, patients may receive either therapy but not both unless due to intolerance within the first month of therapy. Choice of therapy may be based on the toxicity profile and patient preference and/or physician judgment.

While the two agents demonstrated unique side effect profiles, everolimus was associated with lower grade 3/4 toxicity rates compared to SUNItinib. Fatigue, stomatitis, drug-induced pneumonitis and diarrhea were more commonly associated with everolimus, while neutropenia, hypertension, hand-foot syndrome, nausea/diarrhea and stomatitis were seen with SUNItinib. In addition, everolimus and SUNItinib are both oral agents. Either may be used as first-line therapy or in patients previously treated with other therapies such as radiofrequency ablation, transarterial embolization, intraarterial radioisotope injection, and/or chemotherapy.

- **Yttrium-90 for Transarterial Radioembolisation (TARE) of Hepatocellular Cancer (HCC) with Portal Venous Invasion, T3 Tumours, and Metastatic Neuroendocrine Tumours (NETs) (GIYTT) –** Currently, inpatient chemoembolization is the BCCA standard for HCC with T3 tumours, and for metastatic NETs. In patients with HCC with portal venous invasion, chemoembolization is associated with high rates of adverse events. These patients may be suitable to undergo TARE. Although no direct comparison with chemoembolization, large cohort studies suggest that TARE is an acceptable standard therapy for all three populations due to lower incidence and severity of complications. TARE is an outpatient procedure that requires specialized training, and is only currently approved and performed at Vancouver General Hospital (VGH). A written directive is required from a VGH Nuclear Medicine physician in conjunction with VGH Interventional Radiology.

Lung:

- **Gefitinib as First-Line Treatment of Epidermal Growth Factor Receptor (EGFR) Mutation-Positive Advanced NSCLC (ULUAVGEFF) –** In a phase III trial of newly diagnosed NSCLC patients, gefitinib was associated with a significant increase in progression free survival (PFS) when compared to chemotherapy with CARBOplatin and PACLitaxel (6.3 mo vs. 9.5 mo, p<0.001), but not in overall survival (OS) (17.3 mo vs. 18.6 mo, p>0.05) in the subset of patients with EGFR mutation. (*NEJM* 2009;361:947-957) In another phase III trial of metastatic NSCLC patients with EGFR mutation, gefitnib was also associated with significant increase in PFS (5.4 mo vs. 10.8 mo, p<0.001), but not in OS (23.6 mo. vs. 30.5 mo, p=0.31). (*NEJM* 2010;362:2380-2388) Overall, these data suggest significant delay in disease progression but not in prolonging survival.

HIGHLIGHTS OF PROVINCIAL PPO CHANGES

The BCCA will begin the process of revising **Provincial Pre-Printed Orders (PPPOs)** in the month of June. The impetus of change resulted from recent research findings that identified a number of key factors associated with treatment pre-printed orders that can contribute to medication errors.[1] As a result, several recommendations from the Canadian Association of Provincial Cancer Agencies (CAPCA) to improve the safety of chemotherapy pre-printed orders were published earlier this year.[1]

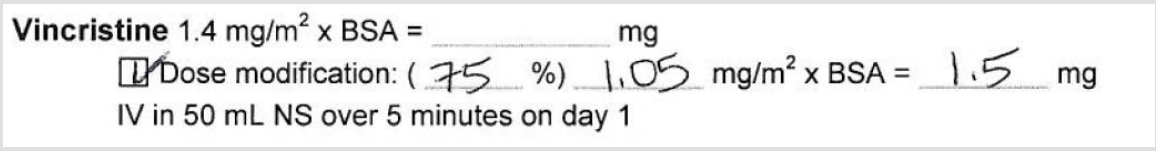
Well-designed protocols and pre-printed orders help simplify and reduce the variability in prescribing between clinicians, and ultimately lead to less potential for medication errors.[2] Pre-printed orders that clearly communicate prescribing information to other healthcare professionals minimize room for interpretation and guesswork, and result in fewer calls to physicians for clarification of orders – the outcome is improved safety and efficiency.

Over time, BC Cancer Agency will incorporate many of the CAPCA recommendations into existing PPPOs. However, a few changes will be made in the short-term that will coordinate with the implementation of new

Dose Error Reduction Systems (DERS) infusion pumps at BCCA.

1. Dose Modifications

The most significant change will be the addition of a "Dose Modification" line that clearly outlines the new dose in "mg/m^2" and the resultant final dose in "mg" to be administered. The reason for this is two-fold – (1) it provides a clear communication of the prescriber's intent for a dose modification, and (2) it allows the nurse an opportunity to double-check the dose modification calculation prior to entering it into the DERS infusion pump. For example, a medication order for vincristine will look as follows:



The intention of the modified dose is clearly communicated as **1.05 mg/m^2** and will be used to input into the DERS pump.

2. Infusion Time

Standardization of medication nomenclature between PPPOs, protocols, DERS infusion pumps and other outputs is essential to avoid misinterpretation errors.[3] To keep the infusion time consistent between the PPPO and the infusion pumps, administration times that are 1 hour or longer will be indicated in hours and minutes. For example:

90 min → 1 hour 30 min
120 min → 2 hours
45 min → 45 min (no change)

In addition, infusion times will specify the shortest time to infuse. To avoid confusion, infusion ranges will no longer be used, unless the infusion time depends on the bag volume. For example:

20-30 min → 20 min
30-60 min → 30 min
"In 100-250 mL NS over 30 min to 1 hour" → No change

Summary:

It is human nature to make mistakes, but the potential for making mistakes can be reduced by using well-designed protocols and PPPOs that effectively communicate the prescriber's intent. Furthermore, the potential for errors can be minimized by ensuring consistency in medication nomenclature across all tools and technology that convey prescribing information. A number of key changes to current Provincial PPOs will help improve consistency and communication, and ultimately increase medication safety.

References:

1. Canadian Association of Provincial Cancer Agencies. *Guidelines for Developing Ambulatory Chemotherapy Preprinted Orders*. Version 1.0 Accessed May 16, 2011. http://www.capca.ca/wp-content/uploads/PPO-Guidelines-FINAL-Jan-9-20111.pdf
2. Institute for Safe Medication Practices (2010). *Guidelines for Standard Order Sets*. Accessed May 16, 2011. http://www.ismp.org/tools/guidelines/StandardOrderSets.pdf
Institute for Safe Medication Practices (2009). *Proceedings from the ISMP Summit on the Use of Smart Infusion Pumps: Guidelines for Safe Implementation and Use*. Accessed May 17, 2011. http://www.ismp.org/tools/guidelines/smartpumps/printerversion.pdf

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Provincial Medication Safety Coordinator
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MEDICATION SAFETY UPDATE

REVISED HAZARDOUS DRUG LIST

The **Provincial Pharmacy Professional Practice Council** has revised the **Pharmacy Directive VI-80** to update the **Hazardous Drug (HD) List** and to delineate the criteria used to assess hazardous drugs. The purpose of the directive is to guide workers in the safe handling of oncology drugs that are considered hazardous.

Initially, the BC Cancer Agency adopted the HD list published by the National Institute for Occupational Safety and Health (NIOSH). This was considered the industry standard in the assessment of hazardous drugs. The BCCA has now evaluated all drugs on the Benefit Drug List, including drugs not on the NIOSH List. The revised Pharmacy Directive VI-80 includes the BCCA NIOSH HD List Addendum which documents the BCCA hazardous drugs not included on the NIOSH HD List. The list will be periodically updated as new drugs become available at the BCCA. It will also be posted as an appendix on the Cancer Drug Manual website (http://www.bccancer.bc.ca/HPI/DrugDatabase/Appendices/default.htm). Institutions in the Communities Oncology Network should refer to local practice recommendations for guidance on safe handling of chemotherapy agents. This applies particularly to drugs that are indicated for both cancer and non-cancer treatments. The BCCA has only evaluated chemotherapy agents for the treatment of cancer.

Background:

Determining the proper precautions to reduce occupational exposure to hazardous drugs is a difficult task. Healthcare workers may be exposed at any point during the procurement, preparation, administration, or disposal of hazardous drugs, through the creation of aerosols, generation of dust, spill management, or exposure to surface contamination. As a result of exposure, workers may experience health effects including skin rash, infertility, miscarriage, birth defects, or secondary cancers. (NIOSH 2004) Health risks may depend on many factors including the inherent toxicity of the drug, the quantity and route of exposure, molecular weight of the drug, and the health status of the individual worker. Exposure risks can be reduced through the development of proper handling procedures for hazardous drugs and the implementation of adequate workplace environmental controls, such as biologic safety cabinets and personal protective equipment (i.e. gloves, gowns, etc.). (NIOSH 2004)

While safety data on hazardous drugs are available, occupational hazard risk assessment by manufacturers is not provided. These data are often gathered from testing in animal models that may use supratherapeutic dosing, and the applicability to humans is unknown. The effects of short- or long-term exposure are also subject to interpretation. The NIOSH working group defined a hazardous drug as a drug that exhibits one or more of the six following characteristics in humans or animals:

1. Carcinogenicity
2. Teratogenicity or other developmental toxicity
3. Reproductive toxicity
4. Organ toxicity at low doses
5. Genotoxicity
6. Structure and toxicity profiles of new drugs that mimic existing drugs deemed hazardous by the above criteria

More details on the application of the 6 characteristics can be found on the revised Pharmacy Directed VI-80.

NURSING UPDATE

FAQ – "FAST PRIMING" OF CHEMOTHERAPY DRUGS FROM IV BAG TO THE PATIENT

Q: "When I'm administering an IV chemotherapy drug that runs at a slow rate (such as a 1st treatment RiTUXimab), can I run the infusion fast at the beginning so the drug gets down the tubing and to the patient faster than at the prescribed, slower start-up rate? There seems to be a delay between initiating the drug infusion and it actually reaching the patient. This can lead to longer chair time for the patient."

A: There is no supporting evidence to suggest that this practice is safe. There is evidence, however, that a drug does NOT necessarily travel in a linear fashion through IV fluid and down the tubing, but rather that it mixes and diffuses with the neutral IV solution in the primary line, thereby potentially reaching the patient much earlier than expected. It is impossible, therefore, to determine exactly when the drug has reached the patient. There have been a few instances of patients reacting to a chemotherapy drug during the priming process, and even reports of a patient showing signs of a reaction even though the line was "just" connected but not running.

For safety reasons, it should be assumed that the patient has full exposure to the drug (and, hence, has the potential to have a reaction) from the time the IV bag is spiked.

All chemotherapy drugs must be infused as specified in the physician's orders. Bolus infusion of IV fluid to prime the line with chemotherapy is unacceptable practice. This is noted in the Directive section of BCCA Nursing Practice Reference C-252.

CANCER DRUG MANUAL

REVISED MONOGRAPHS

CARBOplatin Monograph has been revised to update the Parenteral Administration table to include intraperitoneal administration as a BCCA approved method of administration (see GOOVIPPC). Dosing information has been revised to include the FDA recommended GFR cap of 125 mL/min when calculating initial doses. The *Side Effects* table, and the sections on *Supply and Storage*, and *Solution Preparation and Compatibility* have also been revised to reflect current template standards.

Cyclophosphamide Monograph has been revised to update information on oral solution preparation and dosing in dialysis. The *Side Effects* table, and the sections on *Supply and Storage*, and *Solution Preparation and Compatibility* have also been revised to reflect current template standards.

Gemcitabine Monograph has been revised to update information on dosing in hepatic failure. This includes information concerning fixed-dose rate infusion (FDR) in the setting of increased bilirubin.

IDArubicin Monograph, Patient Handout, and the Chemotherapy Preparation and Stability Chart (CPSC) have undergone complete revisions. Expert review was provided by Dr. Tom Nevill, Dr. John Shepherd and Roberta Esau. IDArubicin is a class I, second generation anthracycline comparable to DAUNOrubicin. IDArubicin or DAUNOrubicin are used in combination with cytarabine as first-line therapy for acute myelogenous leukemia (AML) or as second-line therapy in acute lymphocytic leukemia (ALL).

Highlights of the changes include:

- Revised cardiotoxicity information below the *Side Effects* table to address the early and late cardiotoxic effects
- Clarified conversion factor for calculating cumulative doses
- Revised caution for patients receiving radiation within 2-3 weeks prior to IDArubicin therapy due to increased risk of myelosuppression
- Information on idarubicinol, the active metabolite of IDArubicin, which contributes to IDArubicin's therapeutic efficacy

PACLitaxel Monograph has been revised to update the *Parenteral Administration* table to include intraperitoneal administration as a BCCA approved method of administration (see GOOVIPPC). *Dosage Guidelines* have been updated to include more details on dosing in dialysis. The *Side Effects* table, and the sections on *Supply and Storage,* and *Solution Preparation and Compatibility* have also been revised to reflect current template standards.

NEW EDITORIAL BOARD MEMBERS

The Cancer Drug Manual Team and **Editorial Board** would like to welcome back **Dr. Anna Tinker**, a medical oncologist at the BCCA – Vancouver Centre. The Cancer Drug Manual Team would also like to welcome **Dr. Enny Oetomo** to the Editorial Board as a pharmacist representative for the Communities Oncology Network. Dr. Oetomo is a pharmacist at the BCCA – Vancouver Island Centre.

BENEFIT DRUG LIST

The following programs have been added on the benefit list effective 1 June 2011:

- **Everolimus** (case-by-case) as palliative treatment of advanced pancreatic neuroendocrine tumours (UGIPNEVER)
- **Gefitinib** (case-by-case) as first-line treatment of epidermal growth factor receptor mutation-positive advanced NSCLC
- **Irinotecan** and **Oxaliplatin** (case-by-case) for first-line palliative treatment of metastatic pancreatic cancer (UGIFIRINOX)
- **SUNItinib** (case-by-case) as palliative treatment of advanced pancreatic neuroendocrine tumours (UGIPNSUNI)
- **Yttrium-90** (Class II) for transarterial radioembolisation (TARE) of hepatocellular carcinoma with portal venous invasion, T3 tumours, and metastatic neuroendocrine tumours (GIYTT)

LIST OF NEW AND REVISED PROTOCOLS, PRE-PRINTED ORDERS AND PATIENT HANDOUTS

BC Cancer Agency Protocol Summaries, Provincial Pre-Printed Orders (PPPOs) and Patient Handouts are revised periodically. New, revised or deleted protocols, PPPOs and patient handouts for this month are listed below. Protocol codes for treatments requiring "Compassionate Access Program" (previously Undesignated Indications Request) approval are prefixed with the letter "**U**".

NEW Protocols, PPPOs and Patient Handouts (AFFECTED DOCUMENTS ARE CHECKED):

CODE	Protocol	PPPO	Patient Handout	Protocol Title
GIYTT	☑	☐	☐	Yttrium-90 for Transarterial Radioembolisation (TARE)
UGIFIRINOX	☑	☑	☑	Palliative Combination Chemotherapy for Metastatic Pancreatic Adneocarcinoma Using Irinotecan, Oxalipaltin, Fluorouracil and Folinic Acid (Leucovorin)
UGIPNEVER	☑	☑	☑	Palliative treatment of advanced pancreatic neuroendocrine tumours using Everolimus
UGIPNSUNI	☑	☑	☑	Palliative Treatment of Advanced Pancreatic Neuorendocrine Tumours using SUNItinib
ULUAVGEFF	☐	☑	☑	First-Line Treatment of Epidermal Growth Factor Receptor (EGFR) Mutation-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) with Gefitinib

REVISED PROTOCOLS, PPPOS AND PATIENT HANDOUTS (AFFECTED DOCUMENTS ARE CHECKED):

CODE	Protocol	PPPO	Patient Handout	Changes	Protocol Title
GICART	☐	☑	☐	*Statutory holidays added to Chemotherapy section*	Combined Modality Therapy for Carcinoma of the Anal Canal using Mitomycin, Capecitabine and Radiation Therapy
GICPART	☐	☑	☐	*Statutory holidays added to Chemotherapy section*	Combined Modality Therapy for Carcinoma of the Anal Canal using Cisplatin, Capecitabine and Radiation Therapy
UGICIRB	☐	☑	☐	*Revised Return Appointment Orders section*	Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Irinotecan, Bevacizumab and Capecitabine
UGICOXB	☐	☑	☐	*Revised Return Appointment Orders section*	Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Oxaliplatin, Bevacizumab and Capecitabine.
UGIFFIRB	☐	☑	☐	*Revised Return Appointment Orders section*	Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Irinotecan, Fluorouracil, Folinic Acid (Leucovorin) and Bevacizumab

UGIFFOXB	☐	☑	☐	*Revised Return Appointment Orders section*	Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Oxaliplatin, 5-Fluorouracil, Folinic Acid (Leucovorin) and Bevacizumab
LUAVERL	☑	☐	☐	*Clarified Title, Eligibility and Exclusion Criteria*	Second- or Third-Line Treatment of Advanced Non-Small Cell Lung Cancer (NSCLC) with Erlotinib
ULUAVGEFF	☑	☐	☐	*Revised Eligibility Criteria; updated Tests, Dose Modifications and Precautions*	First-Line Treatment of Epidermal Growth Factor Receptor (EGFR) Mutation-Positive Advanced Non-Small Cell Lung Cancer (NSCLC) with Gefitinib
SAAVGIDD	☑	☐	☐	*Revised Dose Modifications for toxicity*	Treatment of Advanced c-kit Positive Gastrointestinal Stromal Cell Tumours (GIST's) Using 800 mg Dosing of Imatinib (GLEEVEC®)

Website Resources and Contact Information

Website Resources	www.bccancer.bc.ca
Reimbursement & Forms: Benefit Drug List, Class II, Compassionate Access Program	www.bccancer.bc.ca/HPI/ChemotherapyProtocols/Forms
Cancer Drug Manual	www.bccancer.bc.ca/cdm
Cancer Management Guidelines	www.bccancer.bc.ca/CaMgmtGuidelines
Cancer Chemotherapy Protocols, Pre-printed Orders, Protocol Patient Handouts	www.bccancer.bc.ca/ChemoProtocols
Systemic Therapy Program Policies	www.bccancer.bc.ca/HPI/ChemotherapyProtocols/Policies
Systemic Therapy Update	www.bccancer.bc.ca/HPI/ChemotherapyProtocols/stupdate
CON Pharmacy Educators	www.bccancer.bc.ca/RS/CommunitiesOncologyNetwork/Educators/Pharmacists

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Nursing Professional Practice	604.877.6000 x 2623		ilundie@bccancer.bc.ca
OSCAR	888.355.0355	604.708.2051	oscar@bccancer.bc.ca
Compassionate Access Program (CAP)	604.877.6277	604.708.2026	cap_bcca@bccancer.bc.ca
Pharmacy Chemotherapy Certification	250.712.3900 x 686741		rxchemocert@bccancer.bc.ca
BCCA-Abbotsford Centre	604.851.4710 Toll Free 877.547.3777		
BCCA-Centre for the Southern Interior	250.712.3900 Toll Free 888.563.7773		
BCCA-Fraser Valley Centre	604.930.2098 Toll Free 800.523.2885		
BCCA-Vancouver Centre	604.877.6000 Toll Free 800.663.3333		
BCCA-Vancouver Island Centre	250.519.5500 Toll Free 800.670.3322		

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