BC Cancer Agency
CARE & RESEARCH

Systemic Therapy Update

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Website access at http://www.bccancer.bc.ca/HPI/ChemotherapyProtocols/stupdate.htm

INSIDE THIS ISSUE

EDITOR'S CHOICE

HIGHLIGHTS OF CHANGES TO PROTOCOLS, PRE-PRINTED ORDERS

Information on Fluorouracil Infusion: These have been revised to conform to the recommendations by the Institute for Safe Medication Practice (ISMP) Canada (see Editor's Choice in the February issue of Systemic Therapy Update for more details). Key changes to prevent medication errors include standardizing information on the total volume and rate of administration that will appear consistently each protocol and corresponding PPPOs and medication labels.

Aprepitant for Emetogenic Protocols: The antiemetic premedications for a number of protocols have been revised. Previously, the antiemetics used are similar for both high moderate and highly emetogenic protocols (i.e., 5-HT3 antagonist plus dexamethasone). With the introduction of aprepitant to SCNAUSEA, a number of previously highly emetogenic protocols have been reclassified as high moderate emetogenic, with aprepitant added as an option to consider as an antiemetic.

For a complete list of the protocols affected, see under List of Revised Protocols in this issue.

REVISED GUIDELINES FOR CHEMOTHERAPY-INDUCED NAUSEA AND VOMITING

The BCCA Guidelines for Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting in Adults (SCNAUSEA) have been updated to include the use of aprepitant in combination with a 5-HT3 antagonist (e.g., ondansetron) and dexamethasone for patients receiving highly emetogenic chemotherapy protocols. Full details on the use of this new agent can be found in this issue's Drug Update.

Guiding Principles Of the BCCA Compassionate Access Program Application Process

The Provincial Systemic Therapy Program and the Tumour Group Council have recently finalised the guiding principles involved in the application process for the BCCA Compassionate Access Program (CAP), previously known as the Undesignated Indication Request. The CAP application process is intended to support flexibility in access to evidence-based treatments and to:

- ensure optimal patient care and safety in the administration of chemotherapy agents
- ensure that drug treatment choices are evidence-based
- ensure fiscal responsibility in utilizing the Provincial Oncology Drug Budget
- maintain the integrity of the Provincial Systemic Therapy drug database

Approval is on a **case-by-case basis** and requires Tumour Group and Systemic Therapy Program agreement that the requested therapy meets these goals. It is up to the prescribing physician to provide literature support for the proposed treatment when a request is made. Approvals must be obtained prior to the patient being booked to receive the drug therapy.

When a CAP application is required

a. A BCCA protocol with the **'U' prefix designation** and eligibility criteria, which stipulates requirement for CAP approval.
b. **No BCCA protocol** is available.
c. The drug(s) are **not on the BCCA Drug Benefit List**
d. Making c**hanges to an existing BCCA treatment protocol** including:
   - substitution of different drugs
   - use of different doses or routes
   - extension to number of cycles/duration
   - expansion to eligibility criteria/indications
e. **Class II** drug(s) being used:
   - as a single agent in an indication for which no BCCA protocol exists, or
   - in combination with other agents for which no BCCA protocol exists, or
   - in a manner that does not fit the specific indications and eligibility listed in BCCA protocols and on the Class II form
f. **Class I** drug(s) being used:
   - in combination with radiation for which no BCCA protocol exists
   - in any circumstance where there is no Tumour Group specific palliative protocol of optimal therapies that outlines dosage guidelines for the specific drug(s) as single agents or in combination

For more details (e.g., recurring application, request for follow-up data), please see the full document at www.bccancer.bc.ca/HPI/ChemotherapyProtocols/Forms.

CANCER DRUG MANUAL

The "Sun Sensitivity" Patient Handout has been revised and added to the Cancer Drug Manual Appendix on the web site (www.bccancer.bc.ca/HPI/DrugDatabase/Appendices/default). The handout provides information regarding photosensitivity reactions caused by medication, precautions to take to prevent these reactions and appropriate sunscreen application.

Fulvestrant Monograph and Patient Handout have been developed. Expert review was provided by Dr. Vanessa Bernstein (Breast Tumour Group). Fulvestrant is current licensed for the treatment of locally advanced or metastatic breast cancer in postmenopausal women. At present, fulvestrant is not on the benefit list of the BC Cancer Agency.

Vinca Alkaloid monographs have been revised to conform with changes to BCCA Policy V-40. To avoid inadvertent intrathecal administration, the warning label now states: "WARNING: FOR INTRAVENOUS USE ONLY – FATAL IF GIVEN BY OTHER ROUTES" and applies to vinca alkaloids dispensed in minibag or syringes.

Chemotherapy Preparation and Stability Chart – Vinca Alkaloids have been revised to conform with changes to BCCA Policy V-40.

DRUG UPDATE: APREPITANT FOR HIGHLY EMETOGENIC CHEMOTHERAPY

Aprepitant (EMEND®) is an oral antiemetic agent that is now commercially available in Canada.

Indications:
Aprepitant belongs to a relatively new class of drugs called neurokinin-1 (NK1) receptor antagonists. These drugs block substance P at the NK1 receptors in the emetic centre of the CNS. In patients receiving highly emetogenic chemotherapy, aprepitant has been shown to improve the prevention of acute and delayed chemotherapy-induced emesis (CIE)[1,2] but not nausea[3]. It must be used in addition to dexamethasone and a 5-HT3 antagonist (e.g., ondansetron) and to augment the antiemetic potential of those drugs. Aprepitant is not intended to be used as a single agent or for the treatment of existing nausea or vomiting.

Evidence:
In a Phase III trial involving 530 patients receiving highly emetogenic cisplatin chemotherapy, Hesketh et al. compared standard dual antiemetic therapy (ondansetron and dexamethasone) with dual therapy plus aprepitant for three days.[1] The aprepitant regimen was found to be superior to standard therapy, particularly with delayed phase vomiting which is often most challenging to treat:

	standard therapy + aprepitant	***standard therapy***
complete response overall days 1 to 5	72.7%	53.3%
acute phase	89.2%	78.1%
delayed phase	75.4%	55.8%

BCCA Guidelines:
The BCCA Guidelines for Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting in Adults (SCNAUSEA) have been updated to include the recommendations for use of aprepitant in combination with a 5-HT3 antagonist and dexamethasone for patients receiving Highly Emetogenic Chemotherapy. BCCA Chemotherapy Protocols will indicate which antiemetic protocol is recommended.

The BCCA guidelines recommend a three day regimen of aprepitant together with dexamethasone and ondansetron (or other 5-HT3 antagonist):

	Aprepitant	***Ondansetron***	***Dexamethasone***
Day 1:	125 mg pre-chemo	8 mg pre-chemo	8 – 12 mg pre-chemo and 4 mg on the evening of the chemo
Day 2:	80 mg in the morning		4 mg in the morning and 4 mg in the evening

	Aprepitant	*Ondansetron*	*Dexamethasone*
Day 3:	80 mg in the morning		4 mg in the morning and 4 mg in the evening (may continue through days 4 and 5)

Interactions:
Aprepitant may increase the systemic level of oral corticosteroids by up to 50%. Therefore, the dose of dexamethasone should be reduced when given concurrently as an antiemetic, as indicated by the maximum dose of 12 mg above. However, if corticosteroids are given as part of a chemotherapy regimen (e.g., CHOP), their dose should not be reduced.[4]

Aprepitant inhibits the cytochrome P450 3A4 enzyme (CYP3A4) and may increase the plasma level of drugs (including chemotherapy) metabolized by CYP3A4. Although dose adjustments were not required in the clinical trial setting, the manufacturer suggests caution and careful monitoring. Aprepitant also induces the metabolism of drugs like warfarin which are metabolized by CYP2C9.[5] Hence, patients on concurrent aprepitant and warfarin should have their INRs monitored more closely for two weeks following the start of aprepitant with each chemotherapy cycle.[3]

Finally, aprepitant may increase the metabolism of estrogens and thus reduce the efficacy of oral contraceptives. The manufacturer recommends alternative or supplemental birth control methods during treatment with aprepitant and for one month after the last dose of aprepitant.

Adverse Effects:
Aprepitant is generally well tolerated. Adverse effects reported with an incidence greater than 10% include fatigue, weakness, dizziness, diarrhea, dyspepsia and hiccups.

Availability and Cost:
Like other antiemetics, aprepitant is considered a supportive treatment and therefore not covered by the BCCA Benefit Drug list. Currently, it is not a Pharmacare Benefit drug. Aprepitant is available in a Tri-Pack containing the 3 capsules needed for one chemotherapy cycle (one 125 mg capsule plus two 80 mg capsules) as well as individual strength packages. The wholesale cost for one Tri-Pack is approximately $95. Merck Frosst provides an EMEND® Patient Assistance Program available until 31 March 2008 for patients who require financial assistance. For further information call 1-866-982-5452.

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References

1. Hesketh, PJ, et al. The oral neurokinin-1 antagonist aprepitant for the prevention of chemotherapy-induced nausea and vomiting: a multinational, randomized, double-blind, placebo-controlled trial in patients receiving high-dose cisplatin – The Aprepitant Protocol 052 Study Group. J Clin Oncol 2003;21(22):4112-9.
2. Kris, MG, et al. American Society of Clinical Oncology Guideline for Antiemetics in Oncology: Update 2006. J Clin Oncol 2006;24(18):2932-47.
3. Hesketh, PJ. Prevention and treatment of chemotherapy-induced nausea and vomiting. UpToDate®. Accessed 28 January 2008.
4. Ettinger D. NCCN Practice Guidelines in Oncology-Antiemesis v.3.2008:NCCN;2008.
5. Flemm L. Aprepitant for chemotherapy-induced nausea and vomiting. Clin J Oncol Nurs 2004;8(3):303-30.

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 and revised protocols, PPPOs and patient handouts for this month are listed below. Protocol codes for treatments requiring "Compassionate Access Program" (previously Undesignated Indication Request) approval are prefixed with the letter **U**.

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

CODE	Protocol	PPPO	Patient Handout	Changes	Protocol Title
GIENDO1	☑	☑	☐	*Deleted*	Palliative Therapy of Pancreatic Endocrine Tumors using Carmustine and Fluorouracil
UGIFORAF	☑	☐	☐	*Cycle length clarified*	Therapy for Advanced Hepatocellular Carcinoma Using Sorafenib
SCNAUSEA	☑	☐	☐	*Aprepitant added*	Prevention and Treatment of Chemotherapy-Induced Nausea and Vomiting in Adults

Revised Protocols and Pre-Printed Order Related to Fluorouracil Continuous Infusion

CODE	Protocol	PPPO	Patient Handout	Protocol Title
UGIAJFFOX	☑	☑	☐	Adjuvant Combination Chemotherapy for Stage III Colon Cancer Using Oxaliplatin, 5-Fluorouracil and Folinic Acid (Leucovorin)
GIAJFL	☑	☑	☐	Adjuvant Therapy of Colon Cancer using Fluorouracil Injection and Infusion and Folinic Acid (Leucovorin) Infusion
GIAVFL	☑	☑	☐	Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using 5-Fluorouracil Injection and Infusion and Folinic Acid (Leucovorin) Infusion
GIEFUPRT	☑	☑	☐	Combined Modality Therapy for Locally Advanced Esophageal Cancer using 5 Fluorouracil and Cisplatin
UGIFFIRB	☑	☑	☐	Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Irinotecan, Fluorouracil, Folinic Acid (Leucovorin) and Bevacizumab
UGIFFOXB	☑	☑	☐	Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Oxaliplatin, 5-Fluorouracil, Folinic Acid (Leucovorin) and Bevacizumab
GIFOLFIRI	☑	☑	☐	Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Irinotecan, Fluorouracil and Folinic Acid (Leucovorin)

CODE	Protocol	PPPO	Patient Handout	Protocol Title
UGIFOLFOX	☑	☑	☐	Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Oxaliplatin, 5-Fluorouracil and Folinic Acid (Leucovorin)
GIFUART	☑	☑	☐	Combined Modality Curative Therapy for Carcinoma of the Anal Canal using Mitomycin, Fluorouracil and Radiation Therapy
GIFUC	☑	☑	☐	Palliative Chemotherapy for Upper Gastrointestinal Tract Cancer (Gastric, Esophageal, Gall Bladder Carcinoma and Cholangiocarcinoma) and Metastatic Anal Cancer using Infusional Fluorouracil and Cisplatin
GIFUINF	☑	☑	☐	Palliative Therapy for Metastatic Colorectal Adenocarcinoma using Fluorouracil Infusional Chemotherapy
UGIGAVECF	☑	☑	☐	Palliative Therapy for Metastatic or Locally Advanced Gastric, Esophagogastric Cancer Using Epirubicin, Cisplatin and Infusional 5-Fluorouracil
UGIGDCF	☑	☑	☐	Palliative Treatment of Metastatic or Locally Advanced Gastric, Esophagogastric Junction, or Esophageal Adenocarcinoma using with Docetaxel, Cisplatin and Infusional Fluorouracil
GIGECF	☑	☑	☐	Perioperative Treatment of Resectable Adenocarcinoma of the Stomach, Gastroesophageal Junction or Lower 1/3 Esophagus using Epirubicin, Cisplatin and Infusional Fluorouracil
UGIRAJFFOX	☑	☑	☐	Adjuvant Combination Chemotherapy for Stage III Rectal Cancer Using Oxaliplatin, 5-Fluorouracil and Folinic Acid (Leucovorin)
GIRINFRT	☑	☑	☐	Combined Modality Adjuvant Therapy for High Risk Rectal Carcinoma using Capecitabine, Infusional Fluorouracil and Radiation Therapy
GUFUPRT	☑	☑	☐	Combined Modality Therapy for Squamous Cell Cancer of the Genitourinary System Using Fluorouracil and Cisplatin with Radiation
HNCAFRT	☑	☑	☐	Combined Chemotherapy (Carboplatin and Fluorouracil) and Radiation Treatment for Locally Advanced Squamous Cell Carcinoma of the Head and Neck
HNFURT	☑	☑	☐	Therapy for Combined Modality Therapy for Advanced Head and Neck Cancer Using Mitomycin C, Fluorouracil and Split Course Radiation Therapy
HNFUP	☑	☑	☐	Therapy for Advanced Head and Neck Cancer using Cisplatin and Fluorouracil

Revised Protocols and Pre-Printed Order Related to Emetogenic Chemotherapy

CODE	Protocol	PPPO	Patient Handout	Protocol Title
UBRAVGEMP	☑	☐	☐	Palliative Therapy for Metastatic Breast Cancer Using Cisplatin and Gemcitabine

CODE	Protocol	PPPO	Patient Handout	Protocol Title
UGIGAVECF	☑	☐	☐	Palliative Therapy for Metastatic or Locally Advanced Gastric, Esophagogastric Cancer Using Epirubicin, Cisplatin and Infusional 5-Fluorouracil
UGIGIDCF	☑	☐	☐	Palliative Treatment of Metastatic or Locally Advanced Gastric, Esophagogastric Junction, or Esophageal Adenocarcinoma using with Docetaxel, Cisplatin and Infusional Fluorouracil
GIGECC	☑	☐	☐	Perioperative Treatment of Resectable Adenocarcinoma of the Stomach, Gastroesophageal Junction or Lower 1/3 Esophagus using Epirubicin, Cisplatin and Capecitabine
GIGECF	☑	☐	☐	Perioperative Treatment of Resectable Adenocarcinoma of the Stomach, Gastroesophageal Junction or Lower 1/3 Esophagus using Epirubicin, Cisplatin and Infusional Fluorouracil
UGUAJPG	☑	☐	☐	Adjuvant therapy for urothelial carcinoma using cisplatin and gemcitabine
GUAVPG	☑	☐	☐	Palliative therapy for urothelial carcinoma using cisplatin and gemcitabine
GUMVAC	☑	☐	☐	Therapy for transitional cell cancers of the urothelium using Methotrexate, Vinblastine, Doxorubicin and Cisplatin
UGUNAJPG	☑	☐	☐	Neo-Adjuvant Therapy for Urothelial Carcinoma Using Cisplatin and Gemcitabine
HNAVPG	☑	☐	☐	Treatment of Locoregionally Recurrent and/or Metastatic Nasopharyngeal Cancer with Cisplatin and Gemcitabine
LUAJNP	☑	☐	☐	Adjuvant cisplatin and vinorelbine following resection of non-small cell lung cancer
LUAVPG	☑	☐	☐	Treatment of advanced non-small cell lung cancer (NSCLC) with platinum and gemcitabine
LUCISDOC	☑	☐	☐	First-Line Treatment for Advanced Non-Small Cell Lung Cancer (NSCLC) with cisplatin and docetaxel
LUMMPG	☑	☐	☐	Treatment of malignant mesothelioma with cisplatin and gemcitabine
ULUPAC	☑	☐	☐	Summary for Treatment of Thymoma with Platinum, Doxorubicin, and Cyclophosphamide

WEBSITE RESOURCES

The following are available on the BC Cancer Agency website (www.bccancer.bc.ca) under the Health Professionals Info section:

REIMBURSEMENT AND FORMS: BENEFIT DRUG LIST,	www.bccancer.bc.ca/HPI/ChemotherapyProtocols/Forms

CLASS II, COMPASSIONATE ACCESS PROGRAM (UNDESIGNATED INDICATION)	
CANCER DRUG MANUAL	www.bccancer.bc.ca/cdm
CANCER MANAGEMENT GUIDELINES	www.bccancer.bc.ca/CaMgmtGuidelines
CANCER CHEMOTHERAPY PROTOCOLS	www.bccancer.bc.ca/ChemoProtocols
CANCER CHEMOTHERAPY PRE-PRINTED ORDERS	www.bccancer.bc.ca/ChemoProtocols under the index page of each tumour site
SYSTEMIC THERAPY PROGRAM POLICIES	www.bccancer.bc.ca/HPI/ChemotherapyProtocols/Policies
UNCONVENTIONAL CANCER THERAPIES MANUAL	under Patient/Public Info, Unconventional Therapies

IN TOUCH	www.bccancer.bc.ca	bulletin@bccancer.bc.ca
BC CANCER AGENCY	(604) 877-6000	Toll-Free 1-(800) 663-3333
COMMUNITIES ONCOLOGY NETWORK	Ext 2744	jvenkate@bccancer.bc.ca
EDUCATION RESOURCE NURSE	Ext 2638	nursinged@bccancer.bc.ca
NURSING PROFESSIONAL PRACTICE	Ext 2623	ilundie@bccancer.bc.ca
PHARMACY PROFESSIONAL PRACTICE	Ext 2247	gconcon@bccancer.bc.ca
PROVINCIAL SYSTEMIC THERAPY PROGRAM	Ext 2247	gconcon@bccancer.bc.ca
COMMUNITIES ONCOLOGY NETWORK PHARMACIST	Ext 6277	lkovacic@bcancer.bc.ca
DRUG INFORMATION	Ext 6275	druginfo@bccancer.bc.ca
LIBRARY/CANCER INFORMATION	1-(888)-675-8001 Ext 8003	requests@bccancer.bc.ca
OSCAR HELP DESK	1-(888)-355-0355 Fax (604) 708-2051	oscar@bccancer.bc.ca
COMPASSIONATE ACCESS PROGRAM OFFICE (FORMERLY UNDESIGNATED DRUG APPLICATION OFFICE)	Ext 6277 Fax (604) 708-2026	cap_bcca@bccancer.bc.ca
UPDATE EDITOR	Ext 2288	mdelemos@bccancer.bc.ca
CENTRE FOR THE SOUTHERN INTERIOR (CCSI)	(250) 712-3900	Toll-Free 1-(888) 563-7773
FRASER VALLEY CENTRE (FVCC)	(604) 930-2098	Toll-Free 1-(800) 523-2885
VANCOUVER CENTRE (VCC)	(604) 877-6000	Toll-Free 1-(800) 663-3333
VANCOUVER ISLAND CENTRE (VICC)	(250) 519-5500	Toll-Free 1-(800) 670-3322