Systemic Therapy Update

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EDITOR'S CHOICE

NEW PROGRAMS

The Provincial Systemic Therapy Program has approved the following programs effective 1 October 2014:

Vismodegib for Locally Advanced and Metastatic Basal Cell Carcinoma (USMAVVIS) – There is currently no standard treatment for patients with metastatic or locally advanced basal cell carcinoma who are ineligible for surgery or radiation therapy. The advancing cancer can lead to disfiguring changes in a patient's appearance, resulting in social isolation and decreased quality of life. Thus there is a need for therapies to reduce disease burden and improve quality of life. Approval of this therapy by BCCA is based on a non-randomized, non-comparative study, in which vismodegib was associated with a 30-43% response rate and some dramatic reductions in disease volume. [Sekulic A et al. NEJM 2012;366:2171-2179] Common toxicities included muscle spasms and alopecia.

Patients must be referred to a medical oncologist to be considered for vismodegib. A BCCA Compassionate Access Program application is required for each patient. Because vismodegib is teratogenic, prescribing physicians, dispensing pharmacists and patients must be registered with the ERIVEDGE® Pregnancy Prevention Program (www.erivedge.ca).

Afatinib for Locally Advanced and Metastatic Non-Small Cell Lung Cancer (NSCLC) (ULUAVAFAT) – Currently, gefitinib is the standard tyrosine kinase inhibitor for newly diagnosed locally advanced or metastatic NSCLC with epidermal growth factor receptor (EGFR) mutation. Afatinib is another anti-EGFR tyrosine kinase inhibitor which has been shown to improve the progression free survival of these patients when compared to platinum-based chemotherapy (11.1 vs. 6.9 months; 11.0 vs. 5.6 months, HR 0.28)

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[Sequist LV et al. J Clin Oncol 2013;31:3327-34. Wu YL et al. Lancet Oncol 2014;15:213-22] It is generally well tolerated, with similar side effects to other anti-EGFR tyrosine kinase inhibitor, including diarrhea, rash or acne, and stomatitis. A BCCA Compassionate Access Program application is required for each patient.

DRUG UPDATE

Shortage of Bacillus Calmette-Guérin (BCG) Vaccine – There is currently a national shortage of the BCG vaccine OncoTICE® because the manufacturer, Merck, is experiencing a supply issue. Therefore, OncoTICE® can only be obtained from Merck on allocation. Therefore, the BCCA Systemic Therapy Program recommend the following:

Conservation strategies

Prescribers should submit a prioritization form (www.bccancer.bc.ca/HPI/ChemotherapyProtocols/Forms) with each BCG prescription presented to the pharmacy, indicating the priority of the patient as below:

Priority	*BCG indications*	*Allocations*
1	▪ Patients currently on induction or ▪ Starting induction for high risk disease*	Patients will receive BCG treatment
2	▪ Patients currently on maintenance or ▪ Starting maintenance at 3-6 months post-induction for high risk disease*	Patients will receive BCG treatment if sufficient supply for priority 1 patients
3	▪ Patients starting maintenance at 12-24 months post-induction for high risk disease*	Delay ≥ 1 month, then reassess
4	▪ Patients starting maintenance at > 24 months post-induction and ▪ Any low grade disease	Delay until shortage resolved

** High risk = high grade (G3), carcinoma in situ (CIS) or any T1 tumour*

Use of a reduced BCG dose (one-third of the vial)[1,2] has also been suggested to conserve supply.[3] However, OncoTICE® vials do not contain preservative[4] and are meant for single-use only.[5] Additional manipulations when preparing multiple doses from such vials increases the chance of microbial contamination of the contents. Therefore, use of the same single-use vial for multiple doses is only recommended if it can be prepared safely and during shortages of essential drugs[6]

1. *Preparing inside a biological safety cabinet* is acceptable if all doses are prepared inside a cabinet with air quality of ISO Class 5 using aseptic technique.[5,6] The prepared doses must be used within 2 hours.[4]
2. *Preparing outside a biological safety cabinet* is below the recommended standard which has provision allowing such practice only for a non-hazardous drug and when there is a need for emergency or immediate patient administration.[5] Infection outbreaks have been reported when contents from single-use vials were used for more than one patient,[6] although other contributory factors (e.g., syringe reuse) were usually present.[7] If this practice must be used as a last resort, it should be prepared using a closed system transfer device (e.g., Phaseal®).

See separate documents for detailed process (www.bccancer.bc.ca/HPI/DrugDatabase/DrugIndexPro/BCG).

Alternative therapeutic agents

The following intravesical agents may be considered if BCG is not available for high risk patients (high grade, carcinoma in situ, T1 tumour), in the order of preference based on the level of available evidence. Intravesical mitomycin is already on the BCCA Benefit List. Gemcitabine, epirubicin and docetaxel will be reimbursed by BCCA for this indication during the BCG shortage.

EDITOR'S CHOICE

Preference	*Alternative intravesical agents*	
1.	Electromotive mitomycin (if equipment available)[8]	40 mg via electromotive drug administration*
2.	Standard mitomycin[9]	*Induction*: 40 mg weekly x 6 weeks *Maintenance*: 40 mg monthly x 1 year
3.	Gemcitabine[10,11]	*Induction*: 2000 mg weekly x 6 weeks *Maintenance*: 2000 mg monthly x 10 months
4.	Epirubicin[12]	*Induction*: 50 mg weekly x 6 weeks *Maintenance*: 50 mg weekly x 3 doses, every 3 months x up to 3 years
5.	Docetaxel[13]	*Induction*: 75 mg weekly x 6 weeks *Maintenance*: 75 mg monthly x 1 year

**Pre-transurethral resection of bladder tumour*

The sequential administration of intravesical gemcitabine and docetaxel has been suggested as an alternative.[3] However, this regimen is not included in practice guidelines[14,15] and no published supporting data have been identified.

Future Communication

The BCCA is in regular communication with Merck and will provide further information as it becomes available. We will continue to monitor the situation throughout the province and develop strategy to minimize the disruption to patient care.

References

1. Martínez-Piñeiro JA, et al. Has a 3-fold decreased dose of BCG the same efficacy against recurrences and progression of T1G3 and TIS bladder tumors than the standard dose? J Urol 2005;174(4, Part 1):1242.
2. Oddens J, et al. Final results of an EORTC-GU cancers group randomized study of maintenance BCG in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder. Eur Urol 2013;63:462.
3. Approach for consideration to address shortage of BCG. Bladder Cancer Canada (www.bladdercancercanada.org).
4. Organon Canada Ltd. OncoTICE® Product Monograph, 24 October 2001.
5. USP General Chapter 797: Pharmaceutical compounding - sterile preparations. Rockville, MD: United States Pharmacopeial Convention; 2012.
6. Single-dose/single-use vial position and messages. Centers for Disease Control and Prevention (www.cdc.gov/injectionsafety).
7. Outbreaks and patient notifications in outpatient settings. Centers for Disease Control and Prevention (www.cdc.gov/HAI/settings/outpatient/outbreaks-patient-notifications.html).
8. Di Stasi SM, et al. Electromotive instillation of mitomycin immediately before transurethral resection for patients with primary urothelial non-muscle invasive bladder cancer: a randomised controlled trial. Lancet Oncol 2011;12:871.
9. Au JL, et al. Methods to improve efficacy of intravesical mitomycin. J Natl Cancer Inst 2001;93:597.
10. Jones G, et al. Intravesical gemcitabine for non-muscle invasive bladder cancer. Cochrane Database Syst Rev 2012;1:009294.
11. Addeo R, et al. Randomized phase III trial on gemcitabine versus mytomicin in recurrent superficial bladder cancer. J Clin Oncol 2010;28:543.
12. van der Meijden APM, et al. Intravesical instillation of epirubicin, BCG and BCG plus isoniazid for intermediate and high risk Ta, T1 papillary carcinoma of the bladder. J Urol 2001;166:476.
13. Barlow LJ, et al. Long-term survival outcomes with intravesical docetaxel for recurrent nonmuscle invasive bladder cancer after previous BCG therapy. J Urol 2013;189:834.
14. Canadian guidelines for treatment of non-muscle invasive bladder cancer (http://www.cua.org/guidelines_e.asp).
15. NCCN Clinical Practice Guidelines in Oncology: Bladder cancer (www.nccn.org).

HIGHLIGHTS OF CHANGES TO PROTOCOLS, PRE-PRINTED ORDERS AND PATIENT HANDOUTS

Dose Banding of Infusional Fluorouracil – Effective 1 October 2014, the BC Cancer Agency (BCCA) will implement dose banding for fluorouracil administered by INFUSORS® for Gastrointestinal protocols with a 46-hour infusional fluorouracil treatment:

GIAJFFOX
GIAJFL
GIAVFL
GIFFIRB
UGIFFOXB
UGIFIRINOX
GIFOLFIRI
GIFOLFOX
GIGFOLFIRI
GIRAJFFOX

EDITOR'S CHOICE

Physicians will continue to calculate an individual patient's dose. If the dose is within the range of 3000-5500 mg, Pharmacy will substitute a standardized dose within 200 mg of the prescribed dose. The maximum variation of the dose adjustment for each band is 5% or less (see table below). The drug will be provided in an infusional device that delivers the dose in a 230 mL volume at 5 mL/hour. Doses outside this range will continue to be prepared individually with the exact dose by Pharmacy.

Dose Banding Range	Dose Band INFUSOR (mg)
Less than 3000 mg	Pharmacy to mix specific dose
3000 to 3400 mg	3200 mg
3401 to 3800 mg	3600 mg
3801 to 4200 mg	4000 mg
4201 to 4600 mg	4400 mg
4601 to 5000 mg	4800 mg
5001 to 5500 mg	5250 mg
Greater than 5500 mg	Pharmacy to mix specific dose

Currently, BCCA already uses a form of standardized dosing with the dispensing of oral capecitabine. The dose banding of infusional fluorouracil is implemented to improve patient safety and the efficiency of the drug preparation process. Benefits include fewer dose calculation errors, more timely dispensing and reduced patient waiting times, as well as reduced potential for repetitive strain injuries for staff preparing infusional devices. Similar dose banding is already in use at cancer centres in Alberta, Saskatchewan, Manitoba, Ontario and Newfoundland.

CANCER DRUG MANUAL

NEW MONOGRAPHS AND PATIENT HANDOUTS

Vismodegib Monograph and **Patient Handout** have been developed with expert review provided by Dr. Kerry Savage (medical oncologist) and Robert Tillmanns of the BCCA Skin Tumour Group.

Vismodegib (ERIVEDGE®) is an oral inhibitor of the Hedgehog signalling pathway and it is used for treatment of basal cell carcinoma. The Hedgehog pathway is usually dormant in adult tissues but it is activated in patients with basal cell carcinoma, leading to uncontrolled proliferation of basal skin cells. Although vismodegib is generally well tolerated, it is associated with embryo-fetal toxicities and birth defects. Therefore, it is available only through controlled distribution via the ERIVEDGE ® Pregnancy Prevention Program which requires registration of patients, prescribers and pharmacists. Further information is available at www.erivedge.ca or by calling 1-888-748-8926.

Ramucirumab Interim Monograph has been developed. Ramucirumab is a monoclonal antibody which binds to vascular endothelial growth factor receptor 2 (VEGFR2) and blocks binding of VEGFR ligands, causing reduced tumour vascularity and growth. Its present use is gastric cancer. Ramucirumab is available only through Health Canada Special Access Programme and the BCCA Compassionate Access Program. Toxicities include severe hypertension, arterial thromboembolic events and infusion-related reactions. It is classified as a hazardous drug.

Cancer Drug Manual

Revised Monographs, Patient Handouts and Hazardous Drug List

Daunorubicin Monograph: Infusion rate has been standardized to over 30-45 minutes as per current references

Trastuzumab Monograph and **Patient Handout:** Contraception after treatment completion has been extended from 6 to 7 months due to the long half-life of the drug

Hazardous Drug List: Denosumab has been deleted, based on the recent review by the US National Institute for Occupational Safety and Health.

Benefit Drug List

New Programs

The following programs have been added to the Benefit Drug List effective 1 October 2014:

Protocol Title	Protocol Code	Benefit Status
First-line treatment of epidermal growth factor receptor mutation-positive advanced non-small cell lung cancer with ***Afatinib***	**ULUAVAFAT**	Restricted
Treatment of Metastatic or Locally Advanced Basal Cell Carcinoma Using ***Vismodegib***	**USMAVVIS**	Restricted

Financial Support Drug Program (FSDP)

Filgrastim (NEUPOGEN®) Coverage

Effective 1 October 2014, cancer patients enrolled in the FSDP may be able to receive financial assistance for the purchase of filgrastim (GCSF). Patients approved for the FSDP must also have BC PharmaCare Special Authority for filgrastim use for an appropriate cancer indication before the drug is dispensed. Physicians may apply for BC Pharmacare Special Authority using the Filgrastim (GCSF) Usage Form available on the BCCA website (www.bccancer.bc.ca/HPI/ChemotherapyProtocols/Forms).

Retroactive coverage is not permitted through the FSDP for filgrastim prescriptions filled prior to 1 October 2014, regardless of BC PharmaCare Special Authority preceding this date. Only prescriptions filled at a BC retail pharmacy are eligible for FSDP coverage.

Filgrastim coverage is pro-rated according to the level of FSDP benefit approved by the Canadian Cancer Society and up to the patient's Fair PharmaCare annual deductible. Further information on the FSDP is available on the BCCA website (www.bccancer.bc.ca/RS/CommunitiesOncologyNetwork/Emergency+Aid+Drug+Program).

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
GIAVDOC	☐	☐	☑	Palliative Treatment of Metastatic Esophagogastric Adenocarcinoma with DOCEtaxel
GUAJPG	☐	☐	☑	Adjuvant Therapy for Urothelial Carcinoma Using CISplatin and Gemcitabine (Carboplatin Option)
GUBMITO	☑	☐	☐	Intravesical Therapy for Superficial Transitional Cell Bladder Cancer using Mitomycin
GUNAJPG	☐	☐	☑	Neo-Adjuvant Therapy for Urothelial Carcinoma Using CISplatin and Gemcitabine (Carboplatin Option)
HNSAVFAC	☐	☐	☑	Palliative Therapy for Advanced Salivary Gland Cancers Using Cyclophosphamide, DOXOrubicin and Fluorouracil
HNSAVPAC	☐	☐	☑	Treatment of Advanced Salivary Gland Cancers With Platinum, DOXOrubicin and Cyclophosphamide
HNSAVFUP	☐	☐	☑	Treatment of Advanced Head and Neck Cancer Using CISplatin and Fluorouracil
ULUAVAFAT	☑	☑	☐	First-Line Treatment Of Epidermal Growth Factor Receptor Mutation-Positive Advanced Non-Small Cell Lung Cancer with Afatinib
USMAVVIS	☑	☑	☐	Treatment of Metastatic or Locally Advanced Basal Cell Carcinoma Using Vismodegib

REVISED Protocols, PPPOs and Patient Handouts (affected documents are checked):

CODE	Protocol	PPPO	Patient Handout	Changes	Protocol Title
BRAVABR	☐	☑	☐	*TALLman lettering formatted*	Palliative Therapy for Metastatic Breast Cancer using Nanoparticle, Albumin-Bound (nab)-PACLitaxel
GIAVTZCAP	☑	☑	☐	*Liver function tests and dose modifications updated*	Palliative Therapy of Metastatic Neuroendocrine Cancer using Temozolomide and Capecitabine
GIAJFFOX	☑	☑	☐	*Dose banding of infusional fluorouracil*	Adjuvant Combination Chemotherapy for Stage III and Stage IIB Colon Cancer Using Oxaliplatin, Fluorouracil, and Leucovorin
GIAJFL	☑	☑	☐	*Dose banding of infusional fluorouracil*	Adjuvant Therapy of Colon Cancer using Fluorouracil Injection and Infusion and Folinic Acid (Leucovorin) Infusion
GIAVFL	☑	☑	☐	*Dose banding of infusional fluorouracil*	Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Fluorouracil Injection and Infusion and Leucovorin Infusion

REVISED PROTOCOLS, PPPOS AND PATIENT HANDOUTS (AFFECTED DOCUMENTS ARE CHECKED):					
CODE	**Protocol**	**PPPO**	**Patient Handout**	**Changes**	**Protocol Title**
GIAVPANI	☑	☐	☐	*Management of dermatological toxicity clarified*	Palliative Third Line Treatment of Metastatic Colorectal Cancer Using Panitumumab
GIAVCETIR	☑	☐	☐	*Management of dermatological toxicity clarified*	Third Line Treatment of Metastatic Colorectal Cancer Using Cetuximab in Combination with Irinotecan
GIFFIRB	☑	☑	☐	*Dose banding of infusional fluorouracil*	Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Irinotecan, Fluorouracil, Leucovorin, and Bevacizumab
UGIFFOXB	☑	☑	☐	*Dose banding of infusional fluorouracil*	Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Oxaliplatin, Fluorouracil, Leucovorin, and Bevacizumab
UGIFIRINOX	☑	☑	☐	*Dose banding of infusional fluorouracil*	Palliative Combination Chemotherapy for Advanced Pancreatic Adenocarcinoma Using Irinotecan, Oxaliplatin, Fluorouracil and Folinic Acid (Leucovorin)
GIFOLFIRI	☑	☑	☐	*Dose banding of infusional fluorouracil*	Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Irinotecan, Fluorouracil and Leucovorin
GIFOLFOX	☑	☑	☐	*Dose banding of infusional fluorouracil*	Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Oxaliplatin, Fluorouracil, and Leucovorin
GIGFOLFIRI	☑	☑	☐	*Dose banding of infusional fluorouracil*	Second Line Palliative Combination Chemotherapy for Metastatic Gastric or Esophageal Adenocarcinoma Using Irinotecan, Fluorouracil and Folinic Acid (Leucovorin)
GIRAJFFOX	☑	☑	☐	*Dose banding of infusional fluorouracil*	Adjuvant Combination Chemotherapy for Stage III Rectal Cancer Using Oxaliplatin, Fluorouracil, and Leucovorin
GUAJPG	☑	☑	☐	*Carboplatin option added*	Adjuvant Therapy for Urothelial Carcinoma Using CISplatin and Gemcitabine
GUNAJPG	☑	☑	☐	*Carboplatin option added*	Neo-Adjuvant Therapy for Urothelial Carcinoma Using CISplatin and Gemcitabine
LUAVERL	☐	☑	☐	*Option for dose medication added*	Treatment of Advanced Non-Small Cell Lung Cancer (NSCLC) with Erlotinib
LYCHOPR	☑	☐	☐	*Clarification of dose modifications for hematological toxicity*	Treatment of Lymphoma with DOXOrubicin, Cyclophosphamide, vinCRIStine, predniSONE and riTUXimab
LYCHOPRMTX	☑	☑	☐	*Clarification of dose modifications for hematological toxicity, non-PVC changed to non-DEHP, in-line filter added*	Central Nervous System Prophylaxis with High Dose Methotrexate, CHOP and RiTUXimab in Diffuse Large B-cell Lymphoma
SAAJGI	☐	☐	☑	*Duration of therapy clarified*	Adjuvant Treatment of C-Kit Positive High Risk Gastrointestinal Stromal Cell Tumours Using Imatinib
SAAVIME3	☑	☐	☐	*Non-PVC changed to non-DEHP and in-line filter added for etoposide infusion*	**3-Day Etoposide & Ifosfamide-Mesna for Patients with Advanced Soft Tissue or Bony Sarcomas**

Website Resources and Contact Information

Website Resources	www.bccancer.bc.ca
Systemic Therapy Update	www.bccancer.bc.ca/HPI/ChemotherapyProtocols/stupdate
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
CON Pharmacy Educators	www.bccancer.bc.ca/HPI/Pharmacy/ContactUs.htm

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Nursing Professional Practice	604.877.6000 x 672623		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 North	250.645.7300 Toll Free 888.775.7300		
BCCA-Fraser Valley Centre	604.930.2098 Toll Free 800.523.2885		
BCCA-Sindi Ahluwalia Hawkins Centre for the Southern Interior	250.712.3900 Toll Free 888.563.7773		
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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