Systemic Therapy Update

BC Cancer Agency
CARE + RESEARCH
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For Health Professionals Who Care For Cancer Patients

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EDITOR'S CHOICE

NEW PROGRAMS

The Provincial Systemic Therapy Program has approved the following new program effective 01 February 2013:

Lymphoma:

- **Bendamustine for Relapsed Chronic Lymphocytic Leukemia (ULYCLLBEND) –** Bendamustine is now approved for relapsed or refractory chronic lymphocytic leukemia (CLL) after first-line treatment with fludarabine and riTUXimab (LYFLUDR) and standard second-line treatments, including alkylator-based regimens (i.e. cyclophosphamide, vinCRIStine and prednisone [LYCVP]) and alemtuzumab (ULYALEM). Bendamustine is being introduced as a treatment option based on studies showing non-cross-resistance with fludarabine and standard alkylating agents. Multiple phase II studies reported response rates ranging from about 60% to 90%, with a median duration of response ranging from 6 to 40 months *[Bergmann et al. Haematologica 2005;90:1357-64; Fischer et al. J Clin Oncol. 2011;29:3559-66]*. These results are consistently superior to those of traditional agents, and form the basis for the recent Health Canada approval and the new program at the BCCA. Bendamustine is generally well tolerated with the

primary toxicity being myelosuppression. More information on bendamustine can be found in the BCCA Cancer Drug Manual© monograph.

Of note, the pan-Canadian Oncology Drug Review has recently provided an unfavourable recommendation for the use of bendamustine in relapsed CLL based primarily on one randomized controlled trial that showed no significant additional benefit in progression free survival and overall response rates compared to fludarabine. *[Medgenberg et al. Eur J Cancer 2009 Supp:7(2-3):563]*. However, findings of this study have limited relevance in British Columbia since fludarabine is usually used as first-line treatment rather than in the relapsed/refractory setting.

REVISED PROGRAMS

The Provincial Systemic Therapy Program has revised the following program effective 01 February 2013:

Breast:

- **Extended Endocrine Therapy with 5 Years of Letrozole Following 5 Years of Tamoxifen in Postmenopausal Early Breast Cancer** – The Provincial Systemic Therapy Program has until recently funded 3 years of letrozole after 5 years of tamoxifen (8 years total) as adjuvant endocrine therapy for early breast cancer ("late switch/extended adjuvant"), based on the initial presentation of the MA.17 study. *[Goss et al. NEJM 2003;349:1793-1802]* The Program has now approved 5 years of letrozole after 5 years of tamoxifen (10 years total) based on longer follow-up of the MA.17 study population. *[Jin et al. JCO 2012;30(7):718-721]* This long-term analysis showed superior disease free survival (DFS) (HR 0.52 [95% CI, 0.45 to 0.61]), distant DFS (HR of 0.51 [95% CI, 0.42 to 0.61]) and overall survival (HR of 0.61 [95% CI, 0.52 to 0.71]) with ten years of treatment. Please note that letrozole is the only aromatase inhibitor (AI) approved at the BCCA for extended endocrine therapy at this time. Use of other AIs in this setting will require approval from the BCCA Compassionate Access Program.

  Ten years of endocrine therapy (5 years of letrozole following 5 years of tamoxifen) can be considered for any postmenopausal patient with hormone receptor-positive, non-metastatic breast cancer. However, the benefits are greatest among women with highest risk disease (node-positive or large, high-grade, node-negative cancers, and locally advanced breast cancer). The Breast Tumour Group recommends 8 to 10 years of endocrine therapy, particularly in postmenopausal women with good general health, adequate tolerance of side effects, and high risk for breast cancer recurrence. Women who are already taking extended adjuvant letrozole will have BCCA funding extended to five years of letrozole.

  Note that most postmenopausal women with newly diagnosed, early breast cancer currently receive tamoxifen for 2 to 3 years, followed by 2 to 3 years of an AI for a total of 5 years ("early switch"). In this circumstance, it is unknown whether continuing an AI would provide any additional benefit. Until ongoing studies demonstrate a benefit of five years of an AI after only 2 to 3 years of tamoxifen, the Provincial Systemic Therapy Program will continue to limit funding to 5 years of total endocrine therapy when an "early switch" strategy is employed.

EDITOR'S CHOICE

The following table summarizes BCCA approved endocrine treatment options in postmenopausal, hormone-receptor positive early breast cancer.

Years 1 to 5	Years 6 to 10
Tamoxifen only	▪ Discontinue, or ▪ Letrozole up to 5 yr
AI only	Discontinue
Tamoxifen then AI	Discontinue
AI then tamoxifen	Discontinue

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

Updated BCCA Guidelines for the Use of Erythropoiesis-Stimulating Agents (ESAs) in Patients with Cancer (SCESA):

The BCCA SCESA protocol has been revised to reflect the most up-to-date and evidence-based information from the current American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) guidelines, product monographs and supporting literature.

Highlights of recent changes regarding ESA usage include:

- ESAs may only be considered for palliative purposes in patients experiencing anemia, secondary to concomitant myelosuppressive chemotherapy.
- Red blood cell transfusions are the preferred treatment for the management of anemia in patients with cancer.
- The lowest effective doses of ESAs needed to avoid red blood cell transfusions should be used.
- Adequate iron supplementation and antithrombotic prophylaxis is recommended for patients receiving ESAs.
- ESAs must be discontinued at the end of the chemotherapy treatment.

Highlights of recent changes regarding ESA-associated risks include:

- ESAs may increase the risks of death, cardiovascular events, thromboembolic events and stroke.
- ESAs may shorten overall survival and/or increase the risk of tumour progression or recurrence, as demonstrated in clinical trials in patients with breast, head and neck, lymphoid, cervical, non-small cell lung cancers, and patients with active malignancies not treated with either chemotherapy or radiotherapy.

For more details on the recent changes, please refer to the revised BCCA SCESA protocol.

DRUG UPDATE

DOCETAXEL-ASSOCIATED LUNG TOXICITY

Health Canada has recently issued an adverse reaction alert regarding significant DOCEtaxel-associated respiratory toxicities. As of 31 July 2012, thirty-one cases of DOCEtaxel-associated pneumonitis, interstitial lung disease, lung infiltration or respiratory failure have been reported, including 9 fatalities.[1]

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Respiratory symptoms can range from unspecified dyspnea to pulmonary pneumonitis, the latter of which may lead to permanent and potentially fatal pulmonary fibrosis.[2, 3] The time of onset typically occurred between several days after one dose to several weeks after multiple doses. As a result, the Canadian DOCEtaxel product monograph was updated to alert health professionals about these risks, and to promote earlier risk detection and possible intervention. Health Canada recommends that health professionals continue to monitor and report adverse reactions suspected of being associated with DOCEtaxel to the Canada Vigilance Program at 1-866-234-2345. The BCCA is currently reviewing all DOCEtaxel-containing documents in light of the new Health Canada adverse reaction alert.

References:
1. Canadian Adverse Reaction Newsletter. Docetaxel and serious respiratory-related adverse reactions. January 2013;23(1):4.
2. Briasoulis E, Pavlidis N. Noncardiologenic pulomoary edema: an unusual and serious complication of anticancer therapy. Oncologist 2001;6(2):153-61.
3. Danson S, Blackhall F, Hulse P, et al. Interstitial lung disease in lunch cancer: separating disease progression from treatment effects. Drug Saf 2005;28:103-13.

DRUG SHORTAGES RESOLVED

Pegylated Liposomal DOXOrubicin (CAELYX®):

Recent communication from Janssen Inc. has announced that after a prolonged global shortage, pegylated liposomal DOXOrubicin (CAELYX®) is now available for the treatment of *new* patients in Canada. CAELYX® is indicated for the treatment of epithelial ovarian, primary peritoneal or fallopian tube carcinoma (GOOVLDOX, GOOVPLDC) and Kaposi's Sarcoma (KSLDO). The drug shortage began in August 2011 when problems with the sterilization process were discovered during an inspection of the manufacturing facility, Ben Venue Laboratories. The current supplies of CAELYX® have passed quality assurance processes but will expire in the next two months. Effective March/April 2013, new supplies of CAELYX® will be available from a new manufacturing site.

Currently, there may be limited supplies of CAELYX® in the regional cancer centre pharmacies. It is advisable to consult the regional pharmacy leaders regarding the status of drug supply before ordering CAELYX® for a new patient. For further information about the CAELYX® drug shortage, please see the September 2011 issue of the Systemic Therapy Update.

Thyrotropin Alfa (THYROGEN®):

Effective January 2013, the prolonged global drug shortage of thyrotropin alfa (THYROGEN®) has now been resolved. In a recent announcement, the manufacturer, Genzyme, indicated that the drug is now available in consistent supply.

FATAL BORTEZOMIB INTRATHECAL ADMINISTRATION

All bortezomib preparations from BCCA Pharmacy will now be labeled with the following auxiliary label.

WARNING

For SUBCUTANEOUS or
INTRAVENOUS use only.
FATAL if given by other routes.

This practice change comes from a Health Canada-endorsed safety alert issued on 26 January 2012 about the risk of fatalities following the inadvertent *intrathecal* administration of bortezomib. Three fatalities

Drug Update

have been reported worldwide since bortezomib received its first approval in 2003. The incidents occurred when an intrathecal oncology drug was scheduled to be given at the same time as the intravenous bortezomib administration, and both drugs were given intrathecally. There are no current BCCA protocols that combine the simultaneous use of bortezomib with an intrathecal drug. However, the implementation of the product auxiliary label is a safety measure to minimize the risk for administration errors.

Cancer Drug Manual

Revised Monographs and Patient Handouts

Azacitidine Interim Monograph has been expanded to the full **Monograph.** Expert review was provided by Dr. Tom Nevill (hematologist) and Ms. Judith Nyrose (pharmacist) of the Leukemia/BMT Group of BC.

The monograph now includes:

- Pharmacokinetics table
- Expanded information on special precautions and side effects
- Information on the "air sandwich technique" used for subcutaneous administration (a nursing practice standard endorsed by BCCA and the Canadian Association of Nurses in Oncology)
- Alternate dosing regimens to accommodate treatment interruptions due to weekends and holidays

Highlights in the expanded information include:

- Myelosuppression may be more pronounced in cycles 1 and 2, and incidence may increase with higher doses; febrile neutropenia and neutropenic sepsis have been reported
- Injection site reactions can be significant, including bruising, erythema, itching, and pain at the injection site
- Renal abnormalities have been reported with azacitidine when used in combination with other chemotherapy; azactidine and its metabolites are primarily excreted through the kidneys
- Drug interactions via the cytochrome P450 enzyme system are considered unlikely

Benefit Drug List

New Programs

The following program has been added to the Benefit Drug List effective 01 February 2013:

- Bendamustine (restricted funding) for relapsed or refractory chronic lymphocytic leukemia (ULYCLLBEND)

BENEFIT DRUG LIST

DELETED PROGRAMS

The following programs have been removed from the Benefit Drug List effective 01 February 2013 to reflect current practice:

- Cyclophosphamide, DOXOrubicin and Fluorouracil for the adjuvant treatment of breast cancer (UBRAJCAF)
- Cyclophosphamide, Epirubicin and Fluorouracil for the adjuvant treatment of breast cancer (UBRAJCEF)

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
ULYCLLBEND	☑	☑	☐	Treatment of Relapsed Chronic Lymphocytic Leukemia with Bendamustine
LYGDP	☐	☐	☑	Treatment of Lymphoma with Gemcitabine, Dexamethasone and CISplatin (GDP)

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

CODE	Protocol	PPPO	Patient Handout	Changes	Protocol Title
BRAJFECDT	☐	☑	☐	*Minor typo corrected*	Adjuvant Therapy for Breast Cancer using Fluorouracil, Epirubicin and Cyclophosphamide followed by DOCEtaxel and Trastuzumab
BRAJLET	☑	☐	☐	*Eligibility revised*	Adjuvant Letrozole for Breast Cancer
UBRAVLCAP	☑	☐	☐	*Eligibility revised*	Therapy for Metastatic Breast Cancer Using Capecitabine and Lapatinib
UBRAVTCAP	☑	☐	☐	*Eligibility revised*	Palliative Therapy for Metastatic Breast Cancer Using Trastuzumab and Capecitabine

REVISED PROTOCOLS, PPPOS AND PATIENT HANDOUTS (AFFECTED DOCUMENTS ARE CHECKED):					
CODE	**Protocol**	**PPPO**	**Patient Handout**	**Changes**	**Protocol Title**
BRINFCEF	☐	☐	☑	*Protocol code clarified*	Therapy for Inflammatory Breast Cancer Using Cyclophosphamide, Epirubicin and Fluorouracil
UCNBEV	☑	☐	☐	*Typo corrected under Renal dysfunction*	Palliative Therapy for Recurrent Malignant Gliomas Using Bevacizumab With or Without Concurrent Etoposide or Lomustine
UCNTEMOZMD	☑	☐	☐	*Age limit deleted from Eligibility*	Therapy for Malignant Brain Tumours Using Metronomic Dosing of Temozolomide
GIFFIRB	☑	☐	☐	*Fluorouracil dose escalation deleted; Precaution on cardiac toxicity and DPD deficiency added*	Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Irinotecan, Fluorouracil, Folinic Acid (Leucovorin) and Bevacizumab
UGIFFOXB	☑	☐	☐	*Fluorouracil dose escalation deleted; Precaution on cardiac toxicity updated*	Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Oxaliplatin, 5-Fluorouracil, Folinic Acid (Leucovorin) and Bevacizumab
GIFOLFIRI	☑	☐	☐	*Fluorouracil dose escalation deleted; Precaution on cardiac toxicity and DPD deficiency added*	Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Irinotecan, Fluorouracil and Folinic Acid (Leucovorin)
GIFOLFOX	☑	☐	☐	*Fluorouracil dose escalation deleted; Precaution on cardiac toxicity and DPD deficiency added*	Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Oxaliplatin, 5-Fluorouracil and Folinic Acid (Leucovorin)
GIFUC	☑	☐	☐	*Eligibility revised; Precaution on cardiac toxicity updated; Precaution on DPD deficiency and drug interactions added*	Palliative Chemotherapy for Upper Gastrointestinal Tract Cancer (Gastric, Esophageal, Gall Bladder Carcinoma and Cholangiocarcinoma) and Metastatic Anal Cancer using Infusional Fluorouracil and CISplatin
GIGFOLFIRI	☑	☐	☐	*Eligibility revised; Precaution on cardiac toxicity and DPD deficiency added*	Palliative Combination Chemotherapy for Metastatic Gastric or Esophageal Adenocarcinoma Using Irinotecan, Fluorouracil and Folinic Acid (Leucovorin)
UGIGAJCC	☑	☐	☐	*Eligibility clarified; Precaution on cardiac toxicity updated*	Adjuvant Chemotherapy of Gastric Cancer Patients with D2 Resection (Node Negative) or Ineligible for Adjuvant Chemoradiation, Using CISplatin and Capecitabine
GOOVCAG	☑	☑	☐	*Laboratory Tests revised to remove day 14 lab work*	Treatment of Advanced Ovarian Cancer in Patients Who Have Progressed or Recurred Following First-line Platinum-based Treatment Using CARBOplatin and Gemcitabine

REVISED PROTOCOLS, PPPOS AND PATIENT HANDOUTS (AFFECTED DOCUMENTS ARE CHECKED):					
CODE	**Protocol**	**PPPO**	**Patient Handout**	**Changes**	**Protocol Title**
GOOVIPPC	☐	☑	☐	*Laboratory Test requirement clarified to apply only to day 1, not day 8*	Primary Treatment of Stage III Less Than or Equal to 1 cm Visible Residual Invasive Epithelial Ovarian Cancer or Stage 1 Grade 3 or Stage II Grade 3 Papillary Serous Ovarian Cancer Using Intravenous and Intraperitoneal PACLitaxel and Intraperitoneal CARBOplatin
GOTDLR	☑	☐	☐	*Leucovorin route of administration clarified*	Therapy for Low Risk Gestational Trophoblastic Neoplasia (GO 94 02) Using Methotrexate, Leucovorin and Actinomycin D
ULYALEM	☑	☑	☐	*Revised Eligibility to include subcutaneous route; implemented TALLman lettering*	Treatment of Fludarabine-Refractory B-Chronic Lymphocytic Leukemia (B-CLL) and T-Prolymphocytic Leukemia (T-PLL) with Alemtuzumab
LYHDMRP	☑	☐	☐	*Threshold of methotrexate level clarified*	Treatment of Primary Intracerebral Lymphoma with High Dose Methotrexate and RiTUXimab
LYHDMTXP	☑	☐	☐	*Threshold of methotrexate level clarified*	Treatment of Primary Intracerebral Lymphoma with High Dose Methotrexate
LYHDMTXR	☑	☐	☐	*Threshold of methotrexate level clarified*	Treatment of Leptomeningeal Lymphoma or Recurrent Intracerebral Lymphoma with High Dose Methotrexate
SAIME	☑	☐	☐	*Precautions on extravasation deleted*	Etoposide, Ifosfamide-Mesna for Patients with Newly Diagnosed Ewing's Sarcoma/Peripheral Neuroectodermal Tumor (PNET) or Rhabdomyosarcoma or Advanced Soft Tissue or Bony Sarcomas
SCESA	☑	☐	☐	*Guidelines updated to reflect current international guidelines and recommendations*	Summary Guidelines for Selecting and Monitoring Oncology Patients Using Erythropoiesis-Stimulating Agents (ESAs) (Epoetin and Darbepoetin)

DELETED Protocols, PPPOs and Patient Handouts (AFFECTED DOCUMENTS ARE CHECKED):				
CODE	**Protocol**	**PPPO**	**Patient Handout**	**Protocol Title**
UBRAJCAF	☑	☑	☐	Adjuvant Therapy for Breast Cancer Using Cyclophosphamide, DOXOrubicin and Fluorouracil
UBRAJCEF	☑	☑	☐	Adjuvant Therapy for Breast Cancer Using Cyclophosphamide, Epirubicin and Fluorouracil

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	http://www.bccancer.bc.ca/HPI/Pharmacy/ContactUs.htm

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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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