Systemic Therapy Update

BC Cancer Agency
CARE + RESEARCH
An agency of the Provincial Health Services Authority

September 2017
Volume 20, No. 9

For Health Professionals Who Care For Cancer Patients

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EDITOR'S CHOICE

NEW PROGRAMS

Effective 1 September 2017, the BCCA Provincial Systemic Therapy Program has approved the following programs.

Breast:

Zoledronic Acid for the Treatment of Metastatic Breast Cancer (UBRAVZOL) – The BCCA Breast Tumour Group is introducing zoledronic acid as bisphosphonate therapy option in patients who have been treated for at least 9 doses of pamidronate therapy. In a phase III trial, zoledronic acid given every 3 months was associated with non-inferior incidence of skeletal-related events (22% vs. 23.2%). Treatment related adverse events across both arms were similar.[1] A Compassionate Access Program (CAP) approval is needed.

References:
1. Hortobagyi GN, et al. Continued treatment effect of zoledronic acid dosing every 12 vs 4 weeks in women with breast cancer metastatic to bone. The OPTIMIZE-2 randomized clinical trial. JAMA Oncol. 2017;3(7):906-12.

Paclitaxel with Pertuzumab and Trastuzumab for First-Line Treatment of Advanced HER2-Positive Breast Cancer (BRAVPTRAT) – The Breast Tumour Group has introduced paclitaxel with dual anti-HER2 treatment with pertuzumab and trastuzumab for the first-line treatment of metastatic HER2-positive breast cancer. This regimen can be offered as another taxane option to the currently funded docetaxel with dual anti-

HER2 treatment (BRAVPTRAD). Paclitaxel with pertuzumab and trastuzumab has been shown to be highly active and well tolerated in phase II trial.[1] Note that the regimen to be used at BCCA would be a 3-weekly paclitaxel regimen.

References:
1. Dang C, et al. Phase II study of paclitaxel given once per week along with trastuzumab and pertuzumab in patients with human epidermal growth factor receptor 2–positive metastatic breast cancer. J Clin Oncol 2015;33:442-47.

Gastrointestinal:

Perioperative Treatment of Gastric Cancer with Docetaxel, Oxaliplatin, Fluorouracil (UGIGFLODOC**)** – The BCCA Gastrointestinal Tumour Group is launching this new perioperative chemotherapy regimen for patients with adenocarcinoma of the stomach, gastroesophageal junction, or lower 1/3 of the esophagus. In a phase III trial, this combination was associated with improved overall survival (50 vs. 35 mos) compared to a combination of epirubicin, cisplatin and fluorouracil or capecitabine.[1] Serious adverse events were overall similar between the two arms. However, there was a higher incidence of neutropenia (51% vs. 39%) and infections (18% vs. 9%).

References:
1. Al-Batran SE, et al. Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GE) adenocarcinoma (FLOT4-AIO): a multicenter, randomized phase 3 trial. J Clin Oncol 2017;35(15 supply):4004-4004.

Gynecological

Metronomic Cyclophosphamide for Metastatic Ovarian Cancer (GOOVCYCPO) – The BCCA Gynecological Oncology Group has introduced low-dose daily (metronomic) dosing of oral cyclophosphamide for patients who cannot receive platinum-based therapy and have failed at least two lines of non-platinum treatments. Metronomic oral cyclophosphamide has been shown to offer comparable response rate, progression free survival and overall survival to other chemotherapy in this setting, but with an improved toxicity profile.[1]

References:
1. Ferrandina G, at al. Metronomic oral cyclophosphamide (MOC) in the salvage therapy of heavily treated recurrent ovarian cancer patients: a retrospective, multicenter study. BMC Cancer 2014, 14:947-54.

Melanoma

Vemurafenib with Cobimetinib for BRAF V600 Mutation-Positive Unresectable or Metastatic Melanoma (USMAVVC) – The BCCA Melanoma Tumour Group has introduced the combination therapy of vemurafenib, an oral BRAF-targeted agent, with cobimetinib, an oral MEK-targeted agent. This new regimen offers another first-line treatment option to the currently funded dabrafenib and trametinib (USMAVDT). In a phase III trial, a combination of vemurafenib with cobimetinib was associated with longer overall survival compared to vemurafenib alone (22.3 vs. 17.4 mos, HR 0.70).[1] The magnitude of this benefit is similar to that reported with combination of dabrafenib with trametinib. Further information about the pharmacology and toxicity profile of cobimetinib can be found in the Cancer Drug Manual section below.

A BCCA Compassionate Access Program (CAP) approval is required. Please note that BCCA will only fund ONE COURSE of BRAF/MEK-targeted therapy (single agent or in combination); sequential use of these agents will NOT be funded.

References:
1. Larkin J, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med 2014;371(20):1867-76.

MEDICATION SAFETY CORNER

BCCA PATIENT SAFETY LEARNING SYSTEM ADVERSE DRUG REACTIONS REPORT

Background

Adverse Drug Reactions (ADRs) can occur despite the administration of the right drug, dose, and route, for the right indication. They can affect any patient at any time, and may involve any drug. Health Canada collects information about ADRs through its Canada Vigilance program. However, underreporting of ADRs has been an issue. ADR reporting is also supported by Accreditation Canada through the Medication Management Standard.

In 2014, amendments to the *Canada Food and Drugs Act* were introduced by the *Protecting Canadians from Unsafe Drugs Act (Vanessa's Law)*. These amendments are meant to:

- increase ADR reporting
- improve Health Canada's ability to collect post-market drug safety information
- take appropriate action when a serious risk to health is identified
- better protect patient health and safety, and
- increase consumer confidence in therapeutic products on the market.

What has been done at Provincial Health Services Authority (PHSA)?

PHSA agencies have been reporting serious and unexpected ADRs to Health Canada for many years. In January 2017, a streamlined process using a new Patient Safety Learning System (PSLS) form to facilitate reporting and tracking was launched. Information of the ADRs is forwarded to Health Canada to meet new reporting requirements.

How is BCCA utilizing ADR information gathered?

The BCCA Provincial Systemic Therapy Program has been regularly reviewing the themes and trends of the ADRs reported through PSLS. These reported cases have confirmed the importance and effectiveness of teamwork, good communication, documentation and follow-up. While the reports should not be used to determine the incidence or draw conclusions about the reported drugs, as the ADRs could have been influenced by the patients' underlying conditions and concomitant medications, this information will contribute to Health Canada database to allow for larger population based analysis. In particular, it is essential to document clinical experience with newly marketed medications. All healthcare providers are encouraged to report serious and unexpected ADRs through PSLS.

REVISION OF BCCA TALLMAN LETTERING LIST

Since 2011, BCCA has implemented TALLman lettering as one strategy to prevent errors stemming from selection of look-alike/sound-alike drugs. The BCCA Pharmacy Provincial Directive, "*Use of TALLman Lettering for Medication Nomenclature*", has recently been updated to reflect changes recommended by the US Institute for Safe Medication Practices (ISMP). This updated list is also being adopted by health authorities participating in the Clinical and Systems Transformation (CST) project (Provincial Health Services Authority, Vancouver Coastal Health, Providence Health Care).

Example of new ISMP US recommendations based on targeted look-alike/sound-alike, high-alert medications include[1]:

PAZOPanib/PONATinib

MEDICATION SAFETY CORNER

The incorporation of the revised TALLman list into BCCA documentations and databases will occur gradually over the next few months. BCCA staff may access the revised Directive in the BCCA internal drive at: H:\EVERYONE\Pharmacy\BCCA Pharmacy Directives\VI_RiskManagement\VI-90 Medication Nomenclature.

To learn more about the BCCA TALLman lettering initiative, please see the March 2011 issue of the Systemic Therapy Update.

Reference:
1. ISMP. FDA and ISMP lists of look-alike drug names with recommended tall man letters 2016. Available at: www.ismp.org/Tools/tallmanletters.pdf

BENEFIT DRUG LIST

NEW PROGRAMS

Effective 1 September 2017, these treatment programs have been added to the BCCA Benefit Drug List:

Protocol Title	Protocol Code	Benefit Status
Palliative therapy for metastatic breast cancer using **pertuzumab**, **trastuzumab** (HERCEPTIN), and **paclitaxel** as first-line treatment for advanced breast cancer	**BRAVPTRAT**	Class I
Treatment of acute bone pain secondary to breast cancer metastases using **zoledronic acid**	**UBRAVZOL**	Restricted
Perioperative treatment of resectable adenocarcinoma of the stomach, gastroesophageal junction or lower 1/3 esophagus using **docetaxel**, **oxaliplatin**, infusional **fluorouracil**, and **leucovorin**	**UGIGFLODOC**	Restricted
Palliative therapy for relapsed/progressing epithelial ovarian, primary peritoneal, or fallopian tube carcinoma using metronomic low-dose oral **cyclophosphamide**	**GOOVCYCPO**	Class I
Treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma using **vemurafenib** and **cobimetinib**	**USMAVVC**	Restricted

DELETED PROGRAMS

Effective 1 September 2017, these following treatment programs have been deleted from the BCCA Benefit Drug List. The protocols, PPPOs and patient handouts will be kept on the website until current patients have completed their treatments.

Protocol Title	Protocol Code
Combined modality adjuvant therapy for completely resected gastric adenocarcinoma using **fluorouracil** + folinic acid (**leucovorin**) + radiation therapy	**GIGAIRT**
Palliative therapy for metastatic or locally advanced gastric or esophagogastric cancer using **epirubicin**, **cisplatin** and **capecitabine**	**GIGAVECC**

BENEFIT DRUG LIST

Palliative therapy for metastatic or locally advanced gastric, esophagogastric cancer using **epirubicin**, **cisplatin** and infusional **fluorouracil**	**GIGAVECF**
Perioperative treatment of resectable adenocarcinoma of the stomach, gastroesophageal junction or lower 1/3 esophagus using **epirubicin**, **cisplatin** and infusional **fluorouracil**	**GIGECF**

CANCER DRUG MANUAL

NEW MONOGRAPHS AND PATIENT HANDOUTS

Cobimetinib Monograph and **Patient Handout** have been developed with expert review provided by Dr. Kerry Savage (medical oncologist) and Robert Tillmanns (pharmacist) of the BCCA Skin/Melanoma Tumour Group. Cobimetinib is a selective inhibitor of mitogen-activated extracellular kinases 1 and 2 (MEK1 and MEK2). Cobimetinib is indicated for use in combination with vemurafenib for the treatment of patients with BRAFV600 mutation-positive unresectable or metastatic melanoma. Usual dose is 60 mg (3 x 20 mg tablets) given once daily for 21 consecutive days of a 28 day cycle (refer to BCCA Protocol USMAVVC). Reported adverse events include rash, hepatotoxicity, high blood pressure, hemorrhage, and decreases in left ventricular ejection fraction. In addition, MEK inhibitors exhibit class effects such as serous retinopathy, retinal vein occlusion, as well as creatine phosphokinase (CPK) elevations.

Irinotecan Liposome Interim Monograph has been developed. Irinotecan liposome injection is a formulation of irinotecan encapsulated within a lipid bilayer vesicle or liposome. It is not interchangeable with conventional irinotecan as its pharmacokinetic properties, dosing, and strength are different. Irinotecan liposome injection is available only through Health Canada Special Access Program and the BCCA Compassionate Access Program. Usual dosing is 80 mg/m^2 administered IV every two weeks. Patients with a history or pulmonary toxicity, prior radiation to the abdomen, and Gilbert's syndrome may experience increased toxicity.
Highlights from this document:

- As with conventional irinotecan, patients may experience early or late diarrhea and may require intervention. Patients with severe diarrhea should be monitored for dehydration and be given appropriate fluid and electrolyte replacement as necessary.
- Infusion reactions, primarily consisting of rash, urticaria, periorbital edema, or pruritus have been reported, mostly during the initial treatments with irinotecan liposome. Hypersensitivity reactions, including acute infusion reaction may occur.

Irinotecan liposome has now been added to the **Chemotherapy Preparation and Stability Chart** and the **Hazardous Drug List.**

Plerixafor Monograph has been developed with expert review provided by Dr. Heather Sutherland (oncologist/hematologist) of the Leukemia/BMT Program of British Columbia and Katherine Lacaria (pharmacist, Vancouver General Hospital). Plerixafor is a selective chemokine receptor antagonist used in combination with granulocyte colony stimulating factor to increase hematopoietic stem cell release from the bone marrow into peripheral blood for collection and subsequent autologous transplantation. Plerixafor is given as a daily subcutaneous injection prior to apheresis. Usual dose is 0.24 mg/kg per day (to a maximum dose of 40 mg/day). Dose is reduced for poor renal function. Treatment-related adverse events

CANCER DRUG MANUAL

are usually mild or moderate in severity and include injection site reactions, diarrhea, and nausea. Allergic and vasovagal reactions occur rarely.

Zoledronic Acid Monograph and **Patient Handout** have been developed with expert review provided by Dr. Sophie Sun (medical oncologist) and Khushminder Rai (pharmacist) from the BCCA Breast Tumour Group. Zoledronic acid is a nitrogen-containing IV bisphosphonate used for the treatment of hypercalcemia of malignancy, bone metastases of solid tumours, and osteolytic lesions of multiple myeloma. Usual dose is 4 mg administered intravenously (refer to BCCA protocol UBRAVZOL). Starting dose adjustments are necessary for reduced renal function. To decrease renal toxicity, zoledronic acid should be administered over at least 15 minutes. Common side effects are flu-like symptoms (fever, arthralgia, and myalgia) and renal toxicity. Zoledronic acid is generally well tolerated, however it has been associated with electrolyte disturbances (e.g. hypocalcemia), and rarely with atypical femur fractures and osteonecrosis of the jaw.

REVISED MONOGRAPHS AND PATIENT HANDOUTS

Romidepsin Monograph and Chemotherapy Preparation and Stability Chart

- *Supply and Storage:* added information regarding overfill in new vial format

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 treatment requiring BCCA Compassionate Access Program approval are prefixed with the letter "U".

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

CODE	Protocol	PPPO	Patient Handout	Protocol Title
BRAVPTRAT	☑	☑	☐	Palliative therapy for metastatic breast cancer using pertuzumab, trastuzumab (HERCEPTIN), and paclitaxel as first-line treatment for advanced breast cancer
UBRAVZOL	☑	☑	☐	Treatment of acute bone pain secondary to breast cancer metastases using zoledronic acid
UGIGFLODOC	☑	☑	☑	Perioperative treatment of resectable adenocarcinoma of the stomach, gastroesophageal junction or lower 1/3 esophagus using docetaxel, oxaliplatin, infusional fluorouracil, and leucovorin
UGILAN	☐	☐	☑	Management of functional carcinoid and neuroendocrine tumors of the GI tract using lanreotide (SOMATULINE AUTOGEL)
GOOVCYCPO	☑	☑	☐	Palliative therapy for relapsed/progressing epithelial ovarian, primary peritoneal, or fallopian tube carcinoma using metronomic low-dose oral cyclophosphamide
USMAVVC	☑	☑	☑	Treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma using vemurafenib and cobimetinib

REVISED PROTOCOLS, PPPOS AND PATIENT HANDOUTS (AFFECTED DOCUMENTS ARE CHECKED)					
CODE	**Protocol**	**PPPO**	**Patient Handout**	**Changes**	**Protocol Title**
CNB	☑	☐	☐	*Minor typo corrected*	Suppressive therapy for pituitary adenomas using bromocriptine
CNCAB	☑	☐	☐	*Dose titration clarified*	Suppressive therapy for pituitary adenomas using cabergoline
CNQUIN	☑	☐	☐	*Dose titration clarified*	Suppressive therapy for pituitary adenomas using quinagolide
GIAVTZCAP	☐	☐	☑	*Description of treatment clarified*	Palliative therapy of metastatic neuroendocrine cancer of the pancreas, using temozolomide and capecitabine
GICPART	☐	☐	☑	*Description of treatment clarified*	Curative-intent combined modality therapy for cancer of the anal canal, using cisplatin, capecitabine and radiation therapy.
GIGAJCC	☑	☐	☑	*Minor typo corrected, description of treatment clarified*	Adjuvant chemotherapy of gastric cancer patients with D2 resection (node negative) or ineligible for adjuvant chemoradiation, using cisplatin and capecitabine
GIGAJCPRT	☑	☑	☑	*Exclusions, treatment and appointment schedules, and description of treatment clarified*	Adjuvant chemotherapy of gastric cancer patients with completely resected gastric cancer using cisplatin, capecitabine and radiation therapy
GIGAVCC	☐	☐	☑	*Description of treatment clarified*	Palliative therapy for metastatic or locally advanced gastric, gastroesophageal junction adenocarcinoma, esophageal squamous cell carcinoma, or anal squamous cell carcinoma using cisplatin and capecitabine
GIGAVCCT	☐	☐	☑	*Description of treatment clarified*	Palliative treatment of metastatic or locally advanced gastric, gastroesophageal junction or esophageal adenocarcinoma using cisplatin, capecitabine and trastuzumab (HERCEPTIN)
GIGAVECC	☐	☐	☑	*Description of treatment clarified*	Palliative therapy for metastatic or locally advanced stomach or esophageal cancer using epirubicin, cisplatin and capecitabine
UGIGAVRAMT	☑	☑	☐	*Urinalysis for protein added*	Second-line therapy for metastatic or locally advanced gastric or gastroesophageal junction cancer using weekly paclitaxel and ramucirumab
GIGECC	☐	☐	☑	*Description of treatment clarified*	Treatment of operable cancer of the stomach, stomach-esophagus junction or lower 1/3 esophagus, given before and after surgery, using epirubicin, cisplatin and capecitabine
UGUPCABA	☑	☑	☐	*Corticosteroid option updated*	Palliative therapy for metastatic castration resistant prostate cancer using cabazitaxel and prednisone
GUPDOC	☑	☑	☐	*Corticosteroid option updated*	Palliative therapy for metastatic hormone refractory prostate cancer using docetaxel and prednisone
GUPMX	☑	☑	☐	*Corticosteroid option updated*	Palliative therapy for hormone refractory prostate cancer using mitoxantrone and prednisone
LUAVMTNE	☑	☐	☐	*Eligibility updated*	Maintenance therapy of advanced non-small cell lung cancer with erlotinib after first-line chemotherapy
USMAVVEM	☑	☐	☑	*Exclusion, dose modifications and precautions updated*	Treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma using vemurafenib

The PPPOs of the following trastuzumab protocols have been revised for consistent wording on post-infusion monitoring:

CODE	Protocol Title
BRAJACTT	Adjuvant therapy for breast cancer using doxorubicin and cyclophosphamide followed by paclitaxel and trastuzumab (HERCEPTIN)
BRAJACTTG	Adjuvant therapy for breast cancer using dose dense therapy: doxorubicin and cyclophosphamide followed by paclitaxel and trastuzumab (HERCEPTIN)
BRAJDCARBT	Adjuvant therapy for breast cancer using docetaxel, carboplatin, and trastuzumab (HERCEPTIN)
BRAJTDC	Adjuvant therapy for breast cancer using trastuzumab (HERCEPTIN), docetaxel and cyclophosphamide
BRAJTR	Adjuvant therapy for breast cancer using trastuzumab (HERCEPTIN) following the completion of chemotherapy (sequential)
BRAVTRAD	Palliative therapy for metastatic breast cancer using trastuzumab (HERCEPTIN) and docetaxel as first-line treatment for advanced breast cancer
BRAVTRVIN	Palliative therapy for metastatic breast cancer using trastuzumab (HERCEPTIN) and vinorelbine
BRLAACDT	Treatment of locally advanced breast cancer using doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (HERCEPTIN)

The patient handouts of the following single-agent gastrointestinal protocols have been revised to incorporate toxicities management information from the Cancer Drug Manual:

CODE	Protocol Title
GIA	Palliative therapy for hepatoma using doxorubicin
GIAVDOC	Palliative treatment of metastatic esophagogastric adenocarcinoma with docetaxel
GIAVPANI	Palliative third line treatment of metastatic colorectal cancer using panitumumab
GIGAVTR	Continuation of palliative treatment of metastatic or inoperable, locally advanced gastric or gastroesophageal junction adenocarcinoma using trastuzumab (HERCEPTIN)
GIIR	Palliative chemotherapy for metastatic colorectal cancer using irinotecan
GIIRINALT	Palliative chemotherapy for metastatic colorectal cancer using weekly irinotecan
GIPAJGEM	Adjuvant chemotherapy for pancreatic adenocarcinoma using gemcitabine
GIPGEM	Palliative chemotherapy for pancreatic adenocarcinoma, gallbladder cancer, and cholangiocarcinoma using gemcitabine
GIRALT	Palliative chemotherapy for metastatic colorectal cancer using raltitrexed in patients with previous fluorouracil toxicity
UGIOCTLAR	Symptomatic management of functional carcinoid and neuroendocrine tumors of the GI tract using octreotide (SANDOSTATIN LAR)
UGIPNEVER	Palliative treatment of advanced pancreatic neuroendocrine tumours using everolimus
UGIPNSUNI	Treatment of advanced pancreatic neuroendocrine tumours using sunitinib
UGISORAF	Therapy for advanced hepatocellular carcinoma using sorafenib

Website Resources and Contact Information

Website Resources	www.bccancer.bc.ca
Systemic Therapy Update	www.bccancer.bc.ca/health-professionals/professional-resources/systemic-therapy/systemic-therapy-update
Reimbursement & Forms: Benefit Drug List, Compassionate Access Program	www.bccancer.bc.ca/health-professionals/professional-resources/systemic-therapy
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