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

Effective 1 December 2017, the BC Cancer Provincial Systemic Therapy Program has approved the following programs.

Breast:

Adjuvant Bisphosphonates for Breast Cancer (BRAJZOL, UBRAJPAM) – The BC Cancer Breast Tumour Group is launching adjuvant zoledronic acid and pamidronate for postmenopausal women with stage II or III breast cancer. Bone is the most common site of metastases in breast cancer patients, with roughly 75% of patients with metastatic disease having bony involvement. In a meta-analysis of 26 clinical trials of women with early breast cancer, the use of bisphosphonates in postmenopausal women was associated a 3.3% improvement in 10-year breast cancer mortality (hazard ratio 0.82, 0.73–0.93; 2p=0·002). Zoledronic acid will be used as the primary bisphosphonate for this indication (BRAJZOL), with pamidronate as an alternative for patients who are intolerant to zoledronic acid (UBRAJPAM). The bisphosphonates should be started within 1 year of diagnosis, and repeated every 6 months for up to 5 years.

Reference:
Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. Lancet 2015;386(10001):1353-61.

EDITOR'S CHOICE

Adjuvant Weekly Paclitaxel with Trastuzumab for HER2-positive Breast Cancer (UBRAJTTW) – The BC Cancer Breast Tumour Group is launching the use of adjuvant weekly paclitaxel with trastuzumab for patients with small (≤3 cm), node-negative, HER2-positive breast cancers. These patients have previously been ineligible for the pivotal trials of adjuvant trastuzumab. In a study of 406 patients with HER2+ breast cancer tumors measuring up to 3 cm in greatest dimension, who received weekly paclitaxel and trastuzumab for 12 weeks followed by 9 months of trastuzumab monotherapy, the 3-year survival free from invasive disease was 98.7% (95% CI: 97.6 to 99.8). While this data is from a single phase II trial, this protocol is well recognized as an adjuvant therapy option for patients with lower risk HER2+ breast cancers or in more frail patients who might not be able to tolerate standard trastuzumab-based regimens that contain an anthracycline and/or docetaxel (eg. BRAJTDC, BRAJFECDT, BRAJACTT). After the completion of this protocol, patients would go on to receive BRAJTR as per current standard.

Reference:
Tolaney SM, Barry WT, Dang CT, et al. Adjuvant paclitaxel and trastuzumab for node-negative, HER2-positive breast cancer. N Engl J Med 2015;372:134-41.

Gastrointestinal: two new adjuvant regimens are being introduced for gastric cancer. Both regimens offer alternatives to the currently funded GIGAJCC regimen, at the treating physician's discretion, under the same eligibility criteria.

Adjuvant Oxaliplatin and Capecitabine for the Treatment of Gastric Cancer (GIGAJCOX) – The BC Cancer Gastrointestinal Tumour Group has introduced this new adjuvant chemotherapy regimen for patients with gastric cancer who are ineligible for adjuvant chemoradiation, and for patients with node negative disease after D2 resection. In a phase III trial, adjuvant oxaliplatin and capecitabine was shown to improve overall survival in patients treated with D2 gastrectomy (5-yr OS 78% vs 69% in the observation group).

Adjuvant Oxaliplatin, Fluorouracil, and Leucovorin for the Treatment of Gastric Cancer (GIGAJFFOX) – The BC Cancer Gastrointestinal Tumour Group is also introducing this new adjuvant chemotherapy regimen, in addition to the above GIGAJCOX, for gastric cancer patients ineligible for adjuvant chemoradiation, or node negative patients treated with D2 resection.

Reference:
Noh et al. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. Lancet Oncol 2014;15:1389–96.

DRUG UPDATE

BORTEZOMIB INJECTION

Effective December 1, bortezomib subcutaneous (SC) injection will be prepared as a 2.5 mg/mL concentration, instead of the previous 1 mg/mL concentration. Intravenous (IV) push injection will no longer be a standard option for the administration of bortezomib.

SC administration of bortezomib was introduced in 2011 as an alternative administration route to IV push injection. To minimize potential for error, both SC and IV injections were prepared in the same concentration (1 mg/mL). However, this led to the need for multiple SC injections for a given dose because of the large volumes to be injected. Recent audit at BC Cancer has shown minimal use of the IV push route.

Drug Update

Given that SC administration has a lower incidence of peripheral neuropathy, the option of routine IV push injection has been deleted from all bortezomib protocols and PPPOs and changes have been made to the SC concentration to minimize the number of injections per dose.

Sodium Bicarbonate Injection

After several months of a global shortage of parenteral sodium bicarbonate, sodium bicarbonate injection is now available in consistent supply. Treatment protocols using higher doses of methotrexate use sodium bicarbonate in hydration fluids to alkalinize the urine and thereby prevent renal toxicity. These treatment protocols include LYCHOPRMTX, LYCODOXMR, LYHDMRP, LYHDMTXP, LYHDMTXR, MOHDMTX, SAHDMTX, GOTDEMACO, and GOTDLR. At this time, nursing may resume using injectable sodium bicarbonate in pre- and post-hydration alkalinizing regimens in higher dose methotrexate treatment protocols.

Irinotecan Liposome Injection

Irinotecan liposome (ONIVYDE®) injection is a new drug used for the second line treatment of metastatic pancreatic adenocarcinoma in combination with fluorouracil and leucovorin. Some patients may be receiving this drug through Health Canada's Special Access Programme (SAP) or by commercial supply after the recent approval by Health Canada. Note that the drug dose is expressed differently in the SAP and commercial supply sources (below). Therefore, it is important to confirm which vial supply is being used for a particular treatment and individual, so that a clear differentiation can be made in storage, ordering, selection, and preparation between the two supplies. Irinotecan liposome is not currently a BC Cancer benefit drug.

ONIVYDE®	SAP supply	Commercial supply
Dose per vial	50 mg irinotecan hydrochloride trihydrate	43 mg irinotecan free base
Vial concentration	5 mg/mL irinotecan hydrochloride trihydrate	4.3 mg/mL irinotecan free base
Dosing	80 mg/m^2 irinotecan hydrochloride trihydrate	70 mg/m^2 irinotecan free base

Benefit Drug List

New Programs

Effective 1 December 2017, these treatment programs have been added to the BC Cancer Benefit Drug List:

Protocol Title	Protocol Code	Benefit Status
Adjuvant therapy for breast cancer using weekly **paclitaxel** and **trastuzumab** (HERCEPTIN)	**UBRAJTTW**	**Restricted**
Adjuvant treatment of post-menopausal women using **pamidronate**	**UBRAJPAM**	**Restricted**
Adjuvant treatment of post-menopausal women using **zoledronic acid**	**BRAJZOL**	**Class I**

BENEFIT DRUG LIST

Adjuvant chemotherapy of gastric cancer patients with D2 resection (node negative) or ineligible for adjuvant chemoradiation using **oxaliplatin** and **capecitabine**	**GIGAJCOX**	**Class I**
Adjuvant chemotherapy of gastric cancer patients with D2 resection (node negative) or ineligible for adjuvant chemoradiation using **oxaliplatin**, **fluorouracil**, and **leucovorin**	**GIGAJFFOX**	**Class I**
Palliative therapy for lymphoma using radioimmunotherapy: **rituximab**-priming for **ibritumomab** ^{90}Y (ZEVALIN®)	**ULYRITZ**	**Restricted**

CANCER DRUG MANUAL

NEW MONOGRAPHS AND PATIENT HANDOUTS

The following drugs are currently not funded by BC Cancer. The monographs and handouts are being made available for reference only:

Avelumab Interim Monograph has been developed. Avelumab is a programmed death ligand-1 (PDL-1) inhibitor. By binding to PDL-1, avelumab blocks the interaction of PDL-1 with its receptors, resulting in the restoration of immune responses such as anti-tumour responses. Avelumab is only available through Health Canada Special Access Programme and the BC Cancer Compassionate Access Program. Usual dosing is 10 mg/kg IV, given in a two week cycle. Highlights from this document:

- Commonly reported adverse events include: nausea, diarrhea, decreased appetite, constipation, infusion-related reactions, and vomiting.
- Immune-related adverse reactions affect multiple organ systems and can affect the skin, kidneys, heart, liver, thyroid, etc. Immune-related reactions are reversible and managed based on the severity of the reaction with temporary or permanent drug discontinuation, corticosteroid administration, and/or supportive care.

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

TRC105 (Carotuximab) Interim Monograph has been developed. TRC105 is a monoclonal antibody to endoglin (CD105), a transmembrane receptor that is essential for angiogenesis. By targeting endoglin, TRC105 has been shown to effectively inhibit angiogenesis in murine models. TRC105 is only available through Health Canada Special Access Programme and the BC Cancer Compassionate Access Program. Usual dosing follows a split dose regimen for cycle 1 (3 mg/kg IV on day 1; 7 mg/kg on day 4; and 10 mg/kg on day 8), and then a full dose regimen of 10 mg/kg IV weekly for cycles 2 onwards. Highlights from this document:

- Commonly reported adverse events include: headache, epistaxis and gingival bleeding, telangactasia, fatigue, anemia, and nausea.
- Infusion reactions are reported in ~20% of patients; primarily as rigors, nausea, hypertension, flushing, headache, vomiting, and fever. Reactions mostly occur during the initial infusion. Appropriate premedication is recommended.

TRC105 (carotuximab) has now been added to the **Chemotherapy Preparation and Stability Chart** and the **Hazardous Drug List.**

CANCER DRUG MANUAL

Osimertinib Interim Monograph and **Patient Handout** have been developed with expert review provided by Dr. Christopher Lee (medical oncologist) and Alysha Bharmal (pharmacist) of the BC Cancer Lung Tumour Group. Osimertinib is an oral, irreversible, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor that binds to select mutant forms of EGFR (including T790M), but has limited activity against wild-type EGFR. Due to its wild-type sparing nature, toxicities such as diarrhea and skin rash appear to be less common and less severe when compared to first and second generation EGFR TKIs. The most common adverse effects are diarrhea, rash, dry skin, nail toxicity, and fatigue. Serious side effects include interstitial lung disease, QT interval prolongation and LVEF decrease. Osimertinib is supplied as 40 mg and 80 mg tablets. The usual dose is 80 mg once daily without regard to meals. Grapefruit and grapefruit juice should be avoided during treatment.

REVISED MONOGRAPHS AND PATIENT HANDOUTS

Rituximab Monograph

- Updated: information related to the subcutaneous formulation has been added to *Common Trade name*, *Special Precautions, Side Effect table* and *paragraphs, Supply and Storage, Parenteral Administration table,* and *Dosage Guidelines.*
- Chemotherapy Preparation and Stability Chart

- **azaCITidine** – new brand added (Dr. Reddy's)
- **riTUXimab –** SC formulation added (RITUXAN SC®)

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

BC Cancer 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 BC Cancer 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
UBRAJPAM	☑	☑	☐	Adjuvant treatment of post-menopausal women using pamidronate
UBRAJTTW	☑	☑	☐	Adjuvant therapy for breast cancer using weekly paclitaxel and trastuzumab (HERCEPTIN)
BRAJZOL	☑	☑	☐	Adjuvant treatment of post-menopausal women using zoledronic acid
GIGAJCOX	☑	☑	☑	Adjuvant chemotherapy of gastric cancer patients with D2 resection (node negative) or ineligible for adjuvant chemoradiation using oxaliplatin and capecitabine

NEW PROTOCOLS, PPPOS AND PATIENT HANDOUTS (AFFECTED DOCUMENTS ARE CHECKED)				
CODE	**Protocol**	**PPPO**	**Patient Handout**	**Protocol Title**
GIGAJFFOX	☑	☑	☑	Adjuvant chemotherapy of gastric cancer patients with D2 resection (node negative) or ineligible for adjuvant chemoradiation using oxaliplatin, fluorouracil, and leucovorin
ULYRITZ	☑	☑	☐	Palliative therapy for lymphoma using radioimmunotherapy: rituximab-priming for ibritumomab ^{90}Y (ZEVALIN®)

REVISED PROTOCOLS, PPPOS AND PATIENT HANDOUTS (AFFECTED DOCUMENTS ARE CHECKED)					
CODE	**Protocol**	**PPPO**	**Patient Handout**	**Changes**	**Protocol Title**
BRAJACTW	☐	☑	☐	*Paclitaxel dilution clarified*	Adjuvant therapy for early breast cancer using doxorubicin and cyclophosphamide followed by weekly paclitaxel
GIFIRINOX	☐	☑	☐	*Minor typo corrected*	Palliative combination chemotherapy for advanced pancreatic adenocarcinoma using irinotecan, oxaliplatin, fluorouracil and leucovorin
UGOOVBEVP	☑	☐	☐	*Minor typo corrected*	Treatment of platinum resistant epithelial ovarian cancer with bevacizumab and paclitaxel
UGOOVBEVLD	☑	☐	☐	*Minor typo corrected*	Treatment of platinum resistant epithelial ovarian cancer with bevacizumab and pegylated liposomal doxorubicin (CAELYX)
HNLACETRT	☑	☑	☐	*Bloodwork and appointment section clarified*	Combined cetuximab and radiation treatment for locally advanced squamous cell carcinoma of the head and neck
HNNAVPC	☑	☑	☑	*Tests and hepatotoxicity clarified*	Treatment of recurrent or metastatic nasopharyngeal carcinoma with carboplatin and paclitaxel
UHNOTLEN	☑	☑	☑	*Test, dispensing quantity and precautions updated*	Therapy for locally recurrent or metastatic, RAI-refractory differentiated thyroid cancer using lenvatinib
LULAPE2RT	☐	☑	☐	*Premedications clarified*	Treatment of locally advanced non-small cell lung cancer using alternative dosing of cisplatin and etoposide with radiation therapy
LYCVPR	☐	☑	☐	*Timing of drug administration clarified*	Treatment of Advanced Indolent Lymphoma using Cyclophosphamide, vinCRIStine, predniSONE and riTUXimab (CVP-R)
LYFCR	☐	☑	☐	*Timing of drug administration clarified*	Treatment of chronic lymphocytic leukemia (CLL) or Prolymphocytic leukemia with fludarabine, cyclophosphamide and rituximab
LYFLUDR	☐	☑	☐	*Timing of drug administration clarified*	Treatment of chronic lymphocytic leukemia or prolymphocytic leukemia and relapsed indolent lymphoma with fludarabine and rituximab
LYGDPR	☐	☑	☐	*Timing of drug administration clarified*	Treatment of lymphoma with gemcitabine, dexamethasone and cisplatin with rituximab
ULYRICE	☐	☑	☐	*Minor typo corrected*	Treatment of relapsed or refractory advanced stage aggressive b-cell non-Hodgkin's lymphoma with ifosfamide, carboplatin, etoposide and rituximab
LYRMTN	☐	☑	☐	*Minor typo corrected*	Maintenance rituximab for indolent lymphoma

REVISED PROTOCOLS, PPPOS AND PATIENT HANDOUTS (AFFECTED DOCUMENTS ARE CHECKED)					
CODE	**Protocol**	**PPPO**	**Patient Handout**	**Changes**	**Protocol Title**
MYBORMTN	☑	☑	☐	*Bortezomib administration revised, dosing schedule clarified*	Maintenance therapy of multiple myeloma using bortezomib for patients with the high-risk chromosome abnormality
MYBORPRE	☑	☑	☐	*Bortezomib administration revised, dosing schedule clarified*	Treatment of multiple myeloma using bortezomib, dexamethasone with or without cyclophosphamide as induction pre-stem cell transplant
MYBORPRE	☑	☑	☐	*Bortezomib administration revised, dosing schedule clarified*	Treatment of multiple myeloma using bortezomib, dexamethasone with or without cyclophosphamide as induction pre-stem cell transplant
MYBORREL	☑	☑	☐	*Bortezomib administration revised, dosing schedule clarified*	Treatment of relapsed multiple myeloma using bortezomib, dexamethasone with or without cyclophosphamide
MYMPBOR	☑	☑	☐	*Bortezomib administration revised, dosing schedule clarified*	Treatment of multiple myeloma using melphalan, prednisone and weekly bortezomib with the option of substituting cyclophosphamide for melphalan
MYPAM	☑	☑	☑	*Number of ordered treatments clarified*	Treatment of multiple myeloma with pamidronate

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
Cancer Drug Manual	www.bccancer.bc.ca/health-professionals/professional-resources/cancer-drug-manual
Cancer Management Guidelines	www.bccancer.bc.ca/health-professionals/professional-resources/cancer-management-guidelines
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