Systemic Therapy Update

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

Inside This Issue:

EDITOR'S CHOICE

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

The Provincial Systemic Therapy Program has approved the following treatments effective 01 May 2012:

Breast:

Lapatinib with Capecitabine as First-Line Treatment of HER-2 Positive Metastatic Breast Cancer (UBRAVLCAP) – Combination therapy with lapatinib and capecitabine is currently approved for the second-line treatment of patients with relapsed disease after prior trastuzumab therapy. This is based on a phase III trial that demonstrated improved time-to-progression from 4.4 mo to 8.4 mo when compared to capecitabine alone. [Geyer *et al. NEJM* 2006;355:2733-2743] Because there is consistent evidence to indicate benefit of continued anti-HER2 therapy after progression on trastuzumab, the indication is now expanded to first-line therapy in this patient population. [von Minckwitz *et al. J Clin Oncol* 2009;27:1999-2006] Patients may, therefore, receive a maximum of 2 funded lines of anti-HER2 therapy in the metastatic setting. The COMPLETE trial (NCIC CTG MA.31) is currently underway to evaluate which anti-HER2 agent (lapatinib vs. trastuzumab), in combination with a taxane, is the preferred first-line treatment for HER2-positive metastatic breast cancer.

Gynecology:

Dose-Dense Weekly PACLitaxel with CARBOplatin for the Primary Treatment of Advanced Ovarian Cancer (UGOOVDDCAT) – In a phase III, open-label trial involving 637 patients, weekly PACLitaxel (80 mg/m^2) was associated with improved 3-year overall survival (OS) (72.1% vs. 65.1%, HR 0.75) and progression free survival (PFS) (28 mo vs. 17.2 mo, HR 0.71) compared to the 3-weely PACLitaxel regimen (180 mg/m^2). [Katsumata *et al. Lancet* 2009;374:1331-38] Overall, the incidence of hematologic and non-hematologic toxicities were similar between the two groups, with a slightly higher (but non-statistically significant) rate of grades 3 and 4 neutropenia (92% vs. 88%, p=0.15) with weekly PACLitaxel. Patients randomized to weekly PACLitaxel also had higher rates of dose reductions and delays, with an average PACLitaxel dose intensity of 63 mg/m^2 per week.

Based on the above findings, the BCCA Gynecology Tumour Group recommends weekly PACLitaxel over the 3-weekly regimen. The recommended starting dose will be 70 mg/m^2 to mitigate the myelosuppressive effects. Subsequent doses can be escalated to 80 mg/m^2 at the treating physician's discretion if the first cycle is well tolerated. Note that the dosing of weekly PACLitaxel treatment for advanced ovarian cancer differs from that used for the adjuvant treatment of breast cancer patients. Therefore, please follow the dosing recommendations outlined in the tumour group-specific chemotherapy protocols.

Multiple Myeloma:

Combination treatment with Melphalan, Prednisone and Thalidomide for Newly Diagnosed Patients with Multiple Myeloma, Who are Ineligible for Stem Cell Transplantation (UMYMPT) – In a meta-analysis of six randomized controlled trials involving 1685 patients, melphalan-prednisone-thalidomide was associated with longer OS (39.3 vs. 32.7 mo, HR 0.83) and PFS (20.3 vs. 14.9 mos, HR 0.68) when compared to melphalan-prednisone alone. [Fayers *et al. Blood* 2011;118:1239-47] Newly diagnosed multiple myeloma patients are now eligible for treatment with either melphalan-prednisone-thalidomide (UMYMPT) or melphalan-prednisone-bortezomib (UMYMPBOR). The BCCA recommends UMYMPBOR in preference to UMYMPT due to the heterogeneity of the 6 trials upon which the meta-analysis was based. However, selection of therapy will depend on the ease of administration and the unique toxicity profiles of the two regimens. Thalidomide is administered orally while bortezomib is given as a subcutaneous or intravenous injection. While both drugs can cause peripheral neuropathy and neutropenia, bortezomib is associated with potentially severe diarrhea, and thalidomide is associated with constipation, venous thromboembolism and somnolence.

Due to thalidomide's teratogenicity, prescribers, pharmacies and patients must be registered with the Celgene RevAid® Program in order to prescribe, dispense and access the drug. Multiple myeloma patients who had previously accessed compassionate supply thalidomide through RevAid® will continue to do so.

DRUG UPDATE

DRUG SHORTAGE UPDATES

Sandoz Drug Shortages – Therapeutic Options:

To address the ongoing Sandoz Drug Shortages, the Provincial Systemic Therapy Program has approved the implementation of the following therapeutic options, when necessary, for the supportive care agents below:

Agent	Therapeutic Options
IV Ranitidine	For Ranitidine 50 mg IV 30 min Prior to PACLitaxel Administration, Substitute With: *(listed in order of preference)* 1. Famotidine 20 mg IV 30 minutes pre-PACLitaxel 2. Ranitidine 150 mg PO 2-3 hours pre-PACLitaxel* – if famotidine is unavailable 3. Ranitidine 300 mg PO 45 minutes pre-PACLitaxel* – if patient arrives for chemotherapy appointment and has not taken ranitidine PO ** Patients may purchase and take prior to treatment. Note that ranitidine 150 mg is available over-the-counter without a prescription.* Note: Ranitidine 50 mg IV is expected to yield similar serum concentrations 30 min post-administration as ranitidine 150 mg PO 2-3 h post-administration.
IV Ondansetron	For Ondansetron 8 mg IV in Patients Who Have Difficulty Swallowing Tablets, Substitute With: *(listed in order of preference)* 1. Ondansetron 8 mg orally disintegrating tablets 2. Ondansetron 8 mg (10mL) oral solution
IV DimenhyDRINATE	For DimenhyDRINATE 50 mg IV, Substitute With: *(listed in order of preference)* 1. An injectable anti-nauseant therapeutic alternative 2. DimenhyDRINATE chew tabs, oral liquid, or oral syrup using equivalent doses (i.e. 25-50 mg IV Q4-6H = 25-50 mg PO Q4-6H) – if patient has difficulty swallowing solid tablets 3. IM injection (if available) or PR suppositories – if patient cannot tolerate PO intake

Further information about the Sandoz Drug Shortage can be found in the April 2012 issue of the Systemic Therapy Update.

Pegylated Liposomal DOXOrubicin (CAELYX®):

A review of the current status of the pegylated liposomal DOXOrubicin (CAELYX®) drug supply has confirmed that all existing supplies have been produced in the Ben Venue Laboratories production site. This manufacturing facility has been cited for several problems in quality assurance of the sterilization process. As there are no newly manufactured supplies expected to be available for many more months, the BCCA Provincial Systemic Therapy Program has reconfirmed the existing recommendations published in the September 2011 and December 2011 issues of the Systemic Therapy Update.

These recommendations are that only existing patients should be treated with the existing supplies and

that no new patients be initiated on CAELYX® until newly manufactured supplies are available. Prescribers and pharmacies will continue to collaborate to allocate the stock for patients already booked for treatment. For further information about the CAELYX® drug shortage as well as the affected chemotherapy protocols and treatment alternatives, please see the September 2011 and December 2011 issues of the Systemic Therapy Update.

Sodium Thiosulfate 25%:

Hospira Healthcare Corporation has recently announced that sodium thiosulfate 25% 10 mL vials for injection will not be available at least until June 2013. Sodium thiosulfate 25% is indicated as an antidote for the extravasation of intravenous (IV) mechlorethamine. Because IV mechlorethamine has not been commercially available in Canada for several years, the supply interruption of sodium thiosulfate 25% should not impact oncology patient care.

CANCER DRUG MANUAL

REVISED MONOGRAPHS AND PATIENT HANDOUTS

Bortezomib Monograph has been revised to include the Health Canada warning that intrathecal injections may be fatal. Non-Hodgkin's lymphoma has been added as a Health Canada approved indication in the Uses section, and the Children's Dosing section has also been updated.

Cetuximab Monograph has been revised to clarify recommendations for observation periods post-infusion. A one-hour observation period will follow the end of the 1st and 2nd cetuximab infusions, but may be discontinued for subsequent infusions if reactions do not occur for two consecutive infusions.

DOCEtaxel Monograph, Patient Handout and **Chemotherapy Preparation and Stability Chart** have undergone a comprehensive review to ensure up-to-date information in each document. Expert review was provided by Dr. Caroline Lohrisch (Breast Systemic Group Chair) and Kimberly Kuik (Breast Tumour Group Pharmacist).

Major changes to the Monograph include:

- Removed alcohol abuse cautionary statement from Special Precautions
- Added information on CYP P450 interactions under the Interactions table
- Added Hospira brand as an alternative drug supplier under Supply and Storage
- Added the ethanol content of each brand of DOCEtaxel under Solution Preparation and Compatibility
- Updated hepatic dose modifications according to the current product monographs from Hospira and Sanofi-aventis

The Patient Handout was updated as per the current template standard.

Fluorouracil Monograph has been revised to update dosing information in hepatic failure.

Ondansetron Patient Handout has been revised to include abnormal heart rhythm in the Side Effects table. The theoretical interaction with grapefruit has been deleted due to lack of documented evidence.

BENEFIT DRUG LIST

NEW PROGRAMS

The following programs have been added to the Benefit Drug List effective 01 May 2012:

- **Lapatinib** with **Capecitabine** (restricted funding) for first-line, HER2-positive metastatic breast cancer (UBRAVLCAP)
- **Weekly PACLitaxel** (restricted funding) with **CARBOplatin** for advanced ovarian cancer (UGOOVDDCAT)
- **Thalidomide** (restricted funding) with **Prednisone** and **Melphalan** for newly diagnosed patients with multiple myeloma who are ineligible for stem cell transplantation (UMYMPT)

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
GOENDH	☑	☑	☐	Non-Aromatase Inhibitor Hormonal Treatment of Endometrial Cancer
UGOOVDDCAT	☑	☑	☐	Primary Treatment of Advanced Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Carcinoma Using CARBOplatin and Weekly PACLitaxel

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

CODE	Protocol	PPPO	Patient Handout	Changes	Protocol Title
UBRAJACTW	☐	☐	☑	*Clarified Treatment Plan, Calendar and Side Effects*	Adjuvant Therapy for Early Breast Cancer using DOXOrubicin and Cyclophosphamide followed by Weekly PACLitaxel
UBRAVLCAP	☑	☐	☐	*Expanded Eligibility Criteria to include 1st line metastatic breast cancer*	Therapy for Metastatic Breast Cancer Using Capecitabine and Lapatinib
GIFUART	☑	☑	☑	*Modified mitomycin dosing under Treatment and revised Dosing Modifications section to include mitomcyin*	Combined Modality Curative Therapy for Carcinoma of the Anal Canal using Mitomycin, Fluorouracil and Radiation Therapy

REVISED PROTOCOLS, PPPOS AND PATIENT HANDOUTS (AFFECTED DOCUMENTS ARE CHECKED):					
CODE	**Protocol**	**PPPO**	**Patient Handout**	**Changes**	**Protocol Title**
GIPAJGEM	☑	☑	☐	*Revised Eligibility Criteria and updated References*	Adjuvant Chemotherapy for Pancreatic Adenocarcinoma Using Gemcitabine
GOOVIPPC	☑	☑	☐	*Revised creatinine testing as optional rather than mandatory*	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 Serious Ovarian Cancer Using Intravenous and Intraperitoneal PACLitaxel and Intraperitoneal CARBOplatin
ULUAVPP	☑	☐	☐	*CARBOplatin dosing clarified*	First-Line Treatment of Advanced Non-Small Cell Lung Cancer with Platinum and Pemetrexed
UMYMPT	☑	☐	☐	*Revised Eligibility Criteria*	Treatment of Multiple Myeloma Using Melphalan, Prednisone and Thalidomide

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-Vancouver Centre	604.877.6000 Toll Free 800.663.3333		
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