BC Cancer Agency
CARE & RESEARCH

Systemic Therapy Update

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Website access at http://www.bccancer.bc.ca/HPI/ChemotherapyProtocols/stupdate.htm

INSIDE THIS ISSUE

EDITOR'S CHOICE:

TEMSIROLIMUS FOR RENAL CELL CARCINOMA

The Provincial Systemic Therapy Program of the BC Cancer Agency is pleased to announce the funding of **temsirolimus** for **advanced renal cell carcinoma** (RCC) with poor prognostic features. Temsirolimus is an inhibitor of the mammalian target of rapamycin (mTOR) which is given as a weekly intravenous injection. Poor prognostic features in advanced RCC include:

- Karnofsky Performance Status (KPS) < 80 percent
- serum lactate dehydrogenase >1.5 x upper limit of normal
- serum hemoglobin less than normal
- serum calcium > 2.5 mmol/L (10 mg/dl)
- less than one year between initial diagnosis to interferon therapy

In a large phase III trial, temsirolimus has been shown to improve progression-free and overall survival compared to interferon. Temsirolimus is therefore another first-line option in addition to sunitinib and sorafenib for advanced RCC. The use of these agents in the second-line setting is being investigated in clinical trials and hence is not routinely funded by the BCCA. For more details on the therapeutic role of each of these agents for RCC, see the updated RCC section of the Cancer Management Guidelines (www.bccancer.bc.ca/HPI/CancerManagementGuidelines/Genitourinary/Kidney/Management).

CANCER MANAGEMENT GUIDELINES

The **Genitourinary Tumour Group** has updated the management guidelines on the role of cytoreductive nephrectomy, sorafenib and temsirolimus for advanced ***renal cell cancer*** (www.bccancer.bc.ca/HPI/CancerManagementGuidelines/Genitourinary/Kidney/Management). The group has also updated the frequency of various follow-up procedures for patients with ***germ cell tumours*** (www.bccancer.bc.ca/HPI/CancerManagementGuidelines/Genitourinary/Testis/Management/Followup).

The **Infection Control Committee** has updated the antibiotic guideline for ***febrile neutropenia*** management (www.bccancer.bc.ca/febrileneutropenia), including more details on risk stratification and the use of antibiotics

HIGHLIGHTS OF CHANGES IN PROTOCOLS AND PROVINCIAL PRE-PRINTED ORDERS (PPPOS)

The **Breast Tumour Group** has introduced a new weekly paclitaxel regimen (UBRAVT7) for patients with advanced breast cancer who are intolerant to the regular 3-weekly paclitaxel treatment (BRAVTAX). Note that this new protocol requires approval of the BC Cancer Agency Compassionate Access Program (CAP).

The **Gastrointestinal Tumour Group** has extended the maximum number of treatment cycles in the use of gemcitabine for advanced pancreatic and related tumours (GIPGEM) and the combination regimen with fluorouracil and irinotecan for metastatic colorectal cancer (GIFOLFIRI).

The **Genitourinary Tumour Group** has updated the eligibility in the protocols of sorafenib (UGUSORAF) and temsirolimus (UGUTEM) for advanced renal cell carcinoma. Sorafenib may be considered as an alternative first-line therapy if patients are unsuitable for sunitinib, while temsirolimus should be considered for patients with poor prognostic features.

The **Sarcoma Tumour Group** has updated the protocols and PPPOs for:

- high dose methotrexate treatment of osteosarcoma (SAHDMTX, formerly OSHDMTX)
- combination therapy with etoposide and ifosfamide-mesna for newly diagnosed Ewing's sarcoma/peripheral neuroectodermal tumor or rhabdomyosarcoma, and advanced soft tissue or bony sarcomas (SAIME)

CANCER DRUG MANUAL

Panitumumab (VECTIBIX®) Interim Monograph has been developed. Interim monographs contain basic drug information, as well as preparation and administration instructions.

Chemotherapy Preparation and Stability Chart has been revised with the following:

- New products: panitumumab - note that a 0.2 or 0.22 micron low protein binding in-line filter should be used for administration.

FOCUS ON: OXALIPLATIN HYPERSENSITIVITY REACTIONS

Oxaliplatin (ELOXATIN®) is a third generation platinum agent used in the treatment of colorectal cancer (CRC) in both the adjuvant and metastatic settings. Reports of hypersensitivity reactions (HSR) to oxaliplatin have been increasing in recent years as it has become more widely used.[1] The incidence varies in different publications but may be as high as 13-19%.[2] Severe (grade 3 or 4) reactions occur in 2-3% of the patients.[3]

Manifestations

Most platinum-related HSR appear to be IgE-mediated (type 1 reactions) and tend to occur near the beginning of the infusion, usually after repeat exposure to the drug. However, idiosyncratic reactions to oxaliplatin have also been reported. These have a later onset than type 1 reactions, sometimes occurring several hours after the infusion has been completed.[4-6] Symptoms may include: rash, flushing, pruritis,

edema, dyspnea, hypotension, tachycardia, angioedema, bronchospasm and tongue swelling.[5,7,8] Rarely, HSR may be fatal.[3]

It is important to distinguish between HSR and pharyngolaryngeal dysesthesia (PLD), both of which can occur with oxaliplatin infusions.[10] PLD is a neuropathy characterized by a sensation of discomfort or tightness in the back of the throat and the inability to breathe. It may be accompanied by jaw pain and is often very frightening.[11] Unlike severe HSR, patients have normal oxygen saturation and blood pressure, even though they may feel short of breath.

Prevention

It is difficult to predict which patients are most likely to experience HSR from oxaliplatin. However, they may be more at risk if they have a history of hypersensitivity to other drugs or have been previously treated with other chemotherapy agents. They are also more likely to experience reactions after several cycles of oxaliplatin.[4,9] This differs from the infusion reactions from taxanes or monoclonal antibodies that often occur during the first infusion. Intradermal skin tests for allergy to oxaliplatin are not generally recommended as there have been reports of HSR with negative results.[5] Cross-reactivity between oxaliplatin and other platinum agents is rare.[1]

Routine premedications have not been shown to prevent all occurrences of HSR. Oxaliplatin-containing protocols generally include dexamethasone for prevention of nausea and vomiting which will also provide some protection against HSR. Diphenhydramine may be considered for additional protection. Patients should be monitored carefully for signs of HSR during infusions. They should be warned that symptoms may not occur until after they have returned home. They should seek medical attention immediately if severe reactions occur (i.e., tachycardia, dizziness, dsypnea).

Management

Treatment

Oxaliplatin infusions should be stopped immediately in the event of a reaction,[8,12,13] followed by administration of intravenous (IV) antihistamines and corticosteroids. Different regimens of antihistamines and corticosteroids may be used. The BC Cancer Agency currently recommends hydrocortisone 100mg IV and diphenhydramine 25-50mg IV (SCDRUGRX).[12] Patients experiencing life-threatening symptoms (i.e., angioedema, respiratory distress, hypotension) should be managed symptomatically with epinephrine, bronchodilators,[12] and normal saline if needed.[5,12]

Rechallenge with Premedications Alone

The decision to rechallenge depends on the severity of the reaction.[4] Patients with non-life threatening reactions can be rechallenged by adding premedications prior to subsequent infusions of oxaliplatin[14]:

- Dexamethasone 20mg IV 45 min pre-chemo
- Diphenhydramine 50mg IV 30min pre-chemo
- Ranitidine 50mg IV 30 min pre-chemo

Reducing infusion rates (e.g., from the usual 2 hours to 4-6 hours)[7,15] should also be considered since some patients may develop more severe reactions when rechallenged, despite premedications.

Rechallenge with Desensitization Procedure

The practice of rechallenging after severe life-threatening reactions is usually discouraged, although desensitization protocols have been successful in some patients, including one patient who experienced anaphylaxis.[1,13,16,17] The benefit of continued treatment must be weighed against the risk of severe reactions recurring. The product monograph for oxaliplatin lists rechallenging patients with a history of severe HSR as a contraindication.[3]

Various desensitization protocols using different dilutions and premedications have been reported.[5] Bhargava et al. reported a protocol used successfully in a woman with severe oxaliplatin HSR. The patient was able to tolerate subsequent oxaliplatin infusions without incidence.[17] Doses were given over 4 hours instead of the normal 2 hours, with 100mg of hydrocortisone IV given prior to infusion.

The following is an example of a desensitization protocol, adapted from that reported by Bhargava et al. This protocol has a cautious initial dilution of 1:10,000 and infused over a reasonably short period of time (6 hours)[12,17,18]:

Premedications:
- dexamethasone 20 mg PO q6h x 4 doses beginning 24 hours before chemotherapy
- dexamethasone 20 mg IV 45 minutes pre-chemo
- diphenhydramine 50 mg IV 30 minutes pre-chemo
- ranitidine 50 mg IV 30 minutes pre-chemo

Dilutions for oxaliplatin desensitization
- Mix calculated total dose in 500 mL D5W
- Dilute 0.01 mL of this solution in 100 mL D5W (1:10,000 dilution) and administer over 1 hour
- If tolerated, dilute 0.1 mL of the solution in 100 mL D5W (1:1,000 dilution) and administer over 1 hour
- If tolerated, dilute 1 mL of the solution in 100 mL D5W (1:100 dilution) and administer over 1 hour
- If tolerated, dilute 10 mL of the solution in 100 mL D5W (1:10 dilution) and administer over 1 hour
- If tolerated, administer the remaining solution over 2-4 hours – 4 hours for the first desensitization, then reduce to 2 hours for subsequent desensitizations if well tolerated

Summary

Oxaliplatin plays an important role in the management of colorectal cancer. The incidence of severe HSR to oxaliplatin is low, despite increasing reports of overall HSR to oxaliplatin. Clinicians may choose to continue oxaliplatin in patients who have experienced HSR because of the potential clinical benefits. Options are available to manage HSR including premedications, increased oxaliplatin infusion times and desensitization.

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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 and revised protocols, PPPOs and patient handouts for this month are listed below. Protocol codes for treatments requiring "Compassionate Access Program" (previously Undesignated Indication 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
ULKMDSL	☐	☑	☐	Therapy of Myelodysplastic Syndrome using Lenalidomide
UBRAVT7	☑	☑	☐	Palliative Therapy for Metastatic Breast Cancer using Weekly Paclitaxel

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

CODE	Protocol	PPPO	Patient Handout	Changes	Protocol Title
BRAVCAD	☐	☑	☐	*Reminder to use non-PVC bag added*	Palliative Therapy for Metastatic Breast Cancer Using Docetaxel and Capecitabine
GIFUIP	☑	☐	☐	*Compassionate Access Program approval removed*	Chemotherapy of Pseudomyxoma Peritonei using intraperitoneal Mitomycin and Fluorouracil

CODE	Protocol	PPPO	Patient Handout	Changes	Protocol Title
UGIGAVECC	☑	☐	☐	*Typo corrected in Eligibility and Treatment sections*	Palliative Therapy for Metastatic or Locally Advanced Gastric or Esophagogastric Cancer Using Epirubicin, Cisplatin and Capecitabine
GIPGEM	☑	☐	☐	*Number of treatment cycles extended*	Palliative Chemotherapy for Pancreatic Adenocarcinoma, Gallbladder Cancer, and Cholangiocarcinoma Using Gemcitabine
GIFOLFIRI	☑	☐	☐	*Number of treatment cycles extended*	First Line Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Irinotecan, Fluorouracil and Folinic Acid (Leucovorin)
UGUSORAF	☑	☐	☐	*Eligibility criteria revised*	Palliative Therapy for Renal Cell Carcinoma Using Sorafenib
UGUTEM	☑	☐	☐	*Eligibility criteria revised*	Therapy for Advanced Renal Cancer Using Temsirolimus
ULKCMLD	☑	☐	☐	*Title clarified*	Treatment of Chronic Myeloid Leukemia and Ph+ Acute Lymphoblastic Leukemia Using Dasatinib (SPRYCEL®)
LKCMLI	☑	☐	☐	*Title clarified*	Treatment of Chronic Myeloid Leukemia and Ph+ Acute Lymphoblastic Leukemia Using Imatinib (GLEEVEC®)
OSHDMTX	☑	☐	☐	*Protocol code changed to SAHDMTX (see SAHDMTX)*	Treatment of Osteosarcoma Using High Dose Methotrexate with Leucovorin Rescue
SAHDMTX	☑	☐	☐	*Protocol code changed, reformatted, eligibility clarified, GGD and LDH added to Tests, plasma methotrexate concentration for leucovorin rescue revised, neutropenia added to Precautions*	Treatment of Osteosarcoma Using High Dose Methotrexate with Leucovorin Rescue
SAIME	☑	☐	☐	*Reformatted, dosing for younger patients and references added*	Etoposide, Ifosfamide-Mesna for Patients with Newly Diagnosed Ewing's Sarcoma/Peripheral Neuroectodermal Tumor (PNET) or Rhabdomyosarcoma or Advanced Soft Tissue or Bony Sarcomas

CONTINUING EDUCATION

BC Cancer Agency Annual Cancer Conference is now opened for registration. This 3-day conference, to be held on **20-22 November** at the Westin Bayshore Resort & Marina in Vancouver, is the BC Cancer Agency's premier professional development, learning and networking event.

This year's theme, "*Survivorship: Creating It, Managing It"*, will explore at the issues and challenges of living after cancer, how wellbeing and health is impacted by surviving the cancer experience, and how we can work to minimize and mitigate current and future problems to ensure that survivorship means "living well" after cancer.

Details on the agenda and registration are available at: www.bccancer.bc.ca/HPI/ACC2008.

WEBSITE RESOURCES

The following are available on the BC Cancer Agency website (www.bccancer.bc.ca) under the Health Professionals Info section:

REIMBURSEMENT AND FORMS: BENEFIT DRUG LIST, CLASS II, COMPASSIONATE ACCESS PROGRAM (UNDESIGNATED INDICATION)	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	www.bccancer.bc.ca/ChemoProtocols
CANCER CHEMOTHERAPY PRE-PRINTED ORDERS	www.bccancer.bc.ca/ChemoProtocols under the index page of each tumour site
SYSTEMIC THERAPY PROGRAM POLICIES	www.bccancer.bc.ca/HPI/ChemotherapyProtocols/Policies
UNCONVENTIONAL CANCER THERAPIES MANUAL	under Patient/Public Info, Unconventional Therapies

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OSCAR HELP DESK	1-(888)-355-0355 Fax (604) 708-2051	oscar@bccancer.bc.ca
PHARMACY PROFESSIONAL PRACTICE	Ext 2247	jkippen@bccancer.bc.ca
ABBOTSFORD CENTRE (AC)	(604) 851-4710	Toll-free: 1-(877) 547-3777
CENTRE FOR THE SOUTHERN INTERIOR (CCSI)	(250) 712-3900	Toll-Free 1-(888) 563-7773
FRASER VALLEY CENTRE (FVCC)	(604) 930-2098	Toll-Free 1-(800) 523-2885
VANCOUVER CENTRE (VCC)	(604) 877-6000	Toll-Free 1-(800) 663-3333
VANCOUVER ISLAND CENTRE (VICC)	(250) 519-5500	Toll-Free 1-(800) 670-3322