BC Cancer Agency

Systemic Therapy Update

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

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EDITOR'S CHOICE

SYSTEMIC THERAPY ANNUAL INDEX

The 2005 Systemic Therapy Index is now available on our website.

FOCUS ON ERLOTINIB

Erlotinib (Tarceva®, OSI Pharmaceuticals) has recently been approved by Health Canada as monotherapy for locally advanced or metastatic non-small cell lung cancer (NSCLC) following failure of one or more chemotherapy regimens. Erlotinib is the first agent to demonstrate increased survival when used as a third-line agent for NSCLC. The BC Cancer agency currently allows compassionate access to erlotinib for patients whose disease progresses after standard chemotherapy. For now, use of erlotinib requires approval via the undesignated indication request.(1)

The Health Canada approval is largely based on the results of a phase III study by the National Cancer Institute of Canada Clinical Trials Group called BR21. This placebo controlled, double-blind trial randomized 731 patients to either oral erlotinib 150 mg daily or placebo. The primary study endpoint was overall survival and there was an improvement in median survival of 2 months in the erlotinib arm (6.7 months) compared to the placebo arm (4.7 months). Quality of life scores for cough, pain and dyspnea were also better with erlotinib.(2, 3)

Based on these same data, the Common Drug Review has concluded that erlotinib be recommended for patients with NSCLC after failure of at least one prior chemotherapy regimen, and whose EGFR expression status is positive or unknown.

Pharmacology

Erlotinib is an inhibitor of the epidermal growth factor receptor (EGFR). This receptor is a member of the tyrosine kinase family of receptors that are present in cell membranes. Tyrosine kinase receptors are activated by a variety of growth factors that regulate cell growth. When the receptors are activated, they promote activities such as proliferation, angiogenesis, and inhibition of apoptosis.(4) Some cancer cells lose the ability to turn off

the tyrosine kinase receptor, leading to uncontrolled cell proliferation. EGFR has been reported to be overexpressed in more than 50% of patients with NSCLC.(5)

Adverse effects

Rash, diarrhea, conjunctivitis, vomiting and stomatitis are the adverse effects that led to dose adjustments or discontinuation of medication on the BR21 trial. Of these, rash and diarrhea were the most common.(2) Rash and diarrhea are adverse effects that appear to be associated with EGFR tyrosine kinase inhibitors in general.(6) There is some evidence suggesting that the rash is correlated with efficacy of EGFR inhibitors, although it is not a prerequisite.(7) The development of a rash or diarrhea does not necessitate a dose reduction or discontinuation of erlotinib unless they are severe in nature.(8) Mild diarrhea can usually be managed with loperamide.(8) Mild rash, which may be accompanied by itching, can be treated with topical measures. Examples of topical measures include: keeping the skin clean with mild soaps and using anti-itch products such as Aveeno body wash.(4) If these measures are ineffective, dose adjustments in 50mg increments or discontinuation of erlotinib should be considered. Erlotinib is available in 100 mg and 150 mg tablets.(8)

Drug Interactions

Comprehensive testing for erlotinib interactions has not been done, however the following potential interactions have been identified:

- Potent inhibitors of CYP3A4 (i.e. calcium channel blockers, azole antifungals, macrolide antibiotics, fluoroquinolone antibiotics, some HIV antivirals, and grapefruit juice) may lead to increased plasma levels of erlotinib.(8)
- Potent inducers of CYP3A4 (i.e. barbiturates, carbamazepine, phenytoin, glucocorticoids, pioglitazone, St. John's Wort, and some HIV antivirals) may lead to decreased plasma levels of erlotinib.(8)
- Bleeding and elevations in INR have been reported in patients taking warfarin with erlotinib. The mechanism of this interaction is not known. For those on warfarin, the INR should be followed carefully as the warfarin dose may need close adjustment.(8)

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GRAPEFRUIT JUICE INTERACTIONS

Grapefruit Juice can interact with a number of drugs. Since the first interaction was reported in 1989, the list of drug interactions with grapefruit juice has expanded tremendously. This interaction occurs because of a common metabolic pathway involving a specific isoform of intestinal cytochrome P450 enzyme (CYP3A4).

In the oncology setting, a number of ***oral*** drugs may be affected, including:

- busulfan
- cyclophosphamide
- cyclosporine
- etoposide
- exemestane
- flutamide
- gefitinib
- imatinib
- letrozole
- ondansetron

Grapefruit juice inhibits the CYP3A4 metabolism of these drugs in the intestine and may affect the plasma drug levels. This occurs within 2-4 hours of ingestion and may last for 24-72 hours. It should be noted that the interaction can occur even when grapefruit juice and the oral drug are not taken simultaneously. This is because the recovery of CYP3A4 inhibition depends on the intestinal regeneration of this enzyme, which may take up to three days.

Because of the potentially prolonged effect on plasma drug level, it is best to avoid grapefruit and grapefruit juice starting 3 days before and ending 1 day after the treatment. If it is an on-going medication, grapefruit and grapefruit juice should be avoided for the duration of the treatment

CANCER DRUG MANUAL

Doxorubicin and Epirubicin Monographs and Handouts These have been completely updated. The cardiotoxicity section, in particular, has been extensively revised. It provides information and recommendations for the general prevention and management of anthracycline-related cardiotoxicity. For the epirubicin monograph, the suggested dosing in hepatic failure has changed slightly. The previous version suggested a dose reduction for patients with bilirubin > 25 micromol/L; dose adjustments are now recommended for patients with bilirubin > 20 micromol/L. Finally, where supported by evidence, the information on cardiac toxicity and extravasation has been standardized with doxorubicin.

Grapefruit Juice Interaction Standard information has been added to the monographs and handouts for several oral cancer drugs (**etoposide**, **exemestane**, **gefitinib**, **imatinib**). Monographs and handouts for other oral cancer drugs that may be affected by this interaction will be undergoing similar revisions. For more general information on this drug-food interaction, see under the Editor's Choice in this issue of the Update.

Irinotecan and St. John's Wort Interaction This has been added to the irinotecan monograph and handout. St. John's Wort has been shown to inhibit cytochrome P450 3A4 (CYP3A4) metabolism of irinotecan, leading to decreased plasma levels of the active metabolite SN-38. Hence, concurrent use of irinotecan and St. John's Wort should be avoided.

PATIENT EDUCATION

Patient Handout on Lymphoma Treatment Protocols A new patient handout has been developed for LYCVPR (CVP plus rituximab) protocol. Also, the patient handout for LYCHOPR has been revised to incorporate information on the potential interaction between cyclophosphamide and grapefruit juice. For more general information on this drug-food interaction, see under the Editor's Choice in this issue of the Update.

FREQUENTLY-ASKED PHARMACY QUESTION ON THE BC CANCER AGENCY WEBSITE

Has anyone asked this before? How often do we hear that? Or ask it ourselves?

Beginning in February, 2006, questions most frequently addressed to the BC Cancer Agency's Pharmacy CON Educators and Provincial Drug Information Pharmacists can be found on the BC Cancer Agency website under Regional Services – Communities Oncology Network – Educators – Pharmacists.

Watch for this new information resource, coming soon.

LIST OF NEW AND REVISED PROTOCOLS

The **BC Cancer Agency Protocol Summaries** are revised on a periodic basis. New and revised protocols for this month are listed below. Protocol codes for treatments requiring "Undesignated Indication" approval are prefixed with the letter **U**.

New protocol:

Code	Protocol Name
UBRAJTAC	Adjuvant therapy for breast cancer using cyclophosphamide, doxorubicin and docetaxel
SCDEXA	Dexamethasone as treatment for cerebral edema or CNS swelling

Revised protocols:

Code	Changes	Protocol Name
BRAJACTT	*Information on CNS metastases added*	Adjuvant therapy for breast cancer using doxorubicin and cyclophosphamide followed by paclitaxel and trastuzumab
BRAJACTTG	*Information on CNS metastases added*	Adjuvant Therapy for breast cancer using dose dense therapy: doxorubicin and cyclophosphamide followed by paclitaxel and trastuzumab
BRAJTR	*Information on CNS metastases added*	Adjuvant therapy for breast cancer using trastuzumab following the completion of chemotherapy (sequential)
BRLAACDT	*Information on CNS metastases added*	Treatment of locally advanced breast cancer using doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab
CNMODPCV	*TESTS clarified*	Modified PCV chemotherapy of brain tumours using procarbazine, lomustine (CCNU) and vincristine
UGICIRB	*Monitoring for vital signs clarified*	Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Irinotecan, Bevacizumab and Capecitabine
UGICOXB	*Monitoring for vital signs clarified*	Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Oxaliplatin, Bevacizumab and Capecitabine
UGIFFIRB	*Monitoring for vital signs clarified*	Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Irinotecan, Fluorouracil, Folinic Acid (Leucovorin) and Bevacizumab
UGIFFOXB	*Monitoring for vital signs clarified*	Palliative Combination Chemotherapy for Metastatic Colorectal Cancer Using Oxaliplatin, 5-Fluorouracil, Folinic Acid (Leucovorin) and Bevacizumab

Code	Changes	Protocol Name
GOOVTAX3	*Specific dose modifications added*	Treatment of progressive, platinum-refractory epithelial ovarian carcinoma, primary peritoneal carcinoma or fallopian tube carcinoma using paclitaxel
KSLDO	*Title clarified*	Therapy of Kaposi's sarcoma using pegylated liposomal doxorubicin (Caelyx®)
LUAJNP	*Hematology dose modifications and eligibility clarified*	Adjuvant cisplatin and vinorelbine following resection of stage I, II and IIIA non-small cell lung cancer

LIST OF NEW AND REVISED PRE-PRINTED ORDERS

The **INDEX to BC Cancer Agency Pre-printed Orders** are revised on a periodic basis. The revised pre-printed orders for this month are listed below.

New pre-printed orders:

Code	Protocol Name
UBRAJTAC	Adjuvant therapy for breast cancer using cyclophosphamide, doxorubicin and docetaxel

Revised pre-printed orders:

Code	*Changes*	Protocol Name
GIFUINF	*schedule for return to clinic appointments clarified*	Palliative therapy for metastatic colorectal adenocarcinoma using Fluorouracil infusional chemotherapy
LUAVPG	*clarified CrCl requirement only applies to cisplatin*	Treatment of advanced non-small cell lung cancer (NSCLC) with platinum and gemcitabine
LUMMPG	*clarified CrCl requirement only applies to cisplatin*	Treatment of malignant mesothelioma with cisplatin and gemcitabine
LUMMPPEM	*clarified CrCl requirement only applies to cisplatin*	Treatment of malignant mesothelioma with platinum and pemetrexed (ALIMTA®)
LUPE	*clarified CrCl requirement only applies to cisplatin*	Palliative therapy of selected solid tumours using cisplatin and etoposide
LUPESL	*clarified CrCl requirement only applies to cisplatin*	Treatment for limited stage small cell lung cancer (SCLC) with etoposide and cisplatin (EP) and early thoracic irradiation
LYRITUX	*The first line has been revised to read: "Book Chemo weekly x 4" and on the second line add "RTC ____ weeks".*	Treatment of Lymphoma with single agent Rituximab

CONTINUING MEDICAL EDUCATION

"Sleepless - not just in Seattle. Strategies for improving sleep in patients with cancer".
Colleen Sherriff, RN, Fraser Valley Cancer Center.

The following presentation will be presented by telehealth to our community partners *outside* BCCA on March 22 from 0800-0900 and March 28 from 0730-0830. Presentations are also being arranged for BCCA centers at a later date.

Please call Sandy Yuen at VCH Telehealth 604-875-5415, or email her at sandy.yuen@vch.ca for more information about registering.

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, 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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