

Systemic Therapy Update



BC Cancer Agency

CARE + RESEARCH

An agency of the Provincial Health Services Authority

April 2010
Volume 13, Number 4

For health professionals who care for cancer patients
Available online at www.bccancer.bc.ca/HPI/ChemotherapyProtocols/stupdate

INSIDE THIS ISSUE

- [Editor's Choice](#): Focus On – Tamoxifen and Antidepressant Interactions; Drug Update – PharmaCare Coverage for Aprepitant; Gefitinib for Non-Small Cell Lung Cancer
- [Cancer Drug Manual](#) – Revised: Tamoxifen
- [Benefit Drug List](#) – Anastrozole, Exemestane, Letrozole
- [Provincial Systemic Therapy Policies](#) – Intrathecal Chemotherapy Policy Revised
- [List of New and Revised Protocols, Pre-Printed Orders and Patient Handouts](#): **New**: GICART, GICPART, GIGECC, GIOCTLAR, GIPE, GOENDAI, HNNLAPRT, LUAJPC, LUSCTOP **Revised**: BRAVTRAD, BRAVTRAP, CNIME, UHNCETRT, UHNLACETRT, HNLANPRT, UMYMPBOR **Deleted**: GIPAJFF, HNDE
- [Website Resources and Contact Information](#)

EDITOR'S CHOICE:

FOCUS ON: TAMOXIFEN AND ANTIDEPRESSANT INTERACTIONS

Expanded information about antidepressants and their potential for interaction with tamoxifen has been prepared by the BCCA Provincial Drug Information Service, in collaboration with the Breast Tumour Group and Vancouver Cancer Centre psychiatrists. It can be found at: www.bccancer.bc.ca/HPI/DrugDatabase/DrugIndexPro/Tamoxifen.

Why is this important?

Antidepressants that inhibit the metabolism of tamoxifen to its active metabolite, endoxifen, have the potential to decrease the effectiveness of tamoxifen. Two commonly used selective serotonin reuptake inhibitors (SSRIs), fluoxetine (PROZAC®) and paroxetine (PAXIL®), have been shown to decrease endoxifen levels when given concurrently with tamoxifen.¹ SSRIs and the serotonin norepinephrine reuptake inhibitor (SNRI) venlafaxine (EFFEXOR®) are used for treating a variety of conditions in breast cancer patients, including hot flashes, depression and anxiety. This raised the question of which antidepressants could be recommended for patients receiving tamoxifen.

Mechanism of Interaction

Tamoxifen must undergo hepatic metabolism to become active. The formation of active metabolites, primarily endoxifen, is catalyzed by the cytochrome P450 2D6 (CYP2D6) enzyme in the liver. Therefore, coadministration of drugs that *inhibit* CYP2D6 function may decrease the effectiveness of tamoxifen and lead to an increased recurrence of breast cancer. Antidepressants vary in their ability to inhibit the CYP2D6 enzyme; those with *moderate to strong* inhibition being of the most concern.

Paroxetine (PAXIL®) and fluoxetine (PROZAC®) are strong CYP2D6 inhibitors and have been shown to interact with tamoxifen and should be avoided when possible. Citalopram (CELEXA®) and venlafaxine (EFFEXOR®) are weak inhibitors and can be used more safely with tamoxifen. A table of the CYP2D6 activity of various antidepressants is provided in the BCCA Guide.

Evidence

In theory, inhibition of CYP2D6 could result in the decreased anti-estrogenic activity of tamoxifen and lead to inferior clinical outcomes. This was investigated in two retrospective database studies presented at ASCO last year, with conflicting results reported.^{2,3} Also, a recent retrospective study from Ontario also suggests that the greater risk of breast cancer recurrence with paroxetine may be associated with increased cancer death.

A review of 1,962 women with primary breast cancer from Dutch databases found no increase in breast cancer recurrences, even when drugs considered strong CYP2D6 inhibitors were specifically investigated. In this study only 213 women were receiving tamoxifen and a CYP2D6 inhibitor for more than 60 days. The effect on breast cancer recurrence rate reported may, in part, be explained by the short duration of concomitant medication use.

In contrast, Aubert et al. showed an increased risk of breast cancer recurrence in patients receiving tamoxifen plus a *potent or moderate inhibitor* of CYP2D6. This retrospective study of a US database reviewed patients receiving tamoxifen over a two year period (N=1,298: tamoxifen alone N=945, tamoxifen + CYP2D6 inhibitor N=353). The breast cancer recurrence rate in patients receiving tamoxifen plus a CYP2D6 inhibitor was almost two times higher than in those receiving tamoxifen alone (13.9% vs. 7.5%).

Although both studies have relatively small sample sizes and limited follow-up, Aubert has shown that the possibility exists for this interaction to lead to an increase in breast cancer recurrence. In addition, Kelly et al. recently reported their retrospective review of a prescription database in Ontario of 2430 women aged 66 years or older who were treated with tamoxifen and a SSRI.⁴ Concurrent use of paroxetine and tamoxifen was associated with a significant increase risk of death related to breast cancer (hazard ratio 1.91, 95% confidence interval 1.26 to 2.89). No significant increase in risk was found with fluoxetine, sertraline, fluvoxamine, citalopram or venlafaxine.

Conclusion

Until further evidence is provided, the clinical application of this information is to balance the benefit vs. risk of using a moderate or potent inhibitor of CYP2D6 in patients taking tamoxifen, and to consider the use of an alternative.

Submitted by:

Lynne Ferrier, MBA, BSc. Pharm.
Pharmacy CON Educator
Fraser Valley Centre – BC Cancer Agency

References:

1. Borges S, Desta Z, Li L, et al. Quantitative effect of CYP2D genotype and inhibitors on tamoxifen metabolism: Implication for optimization of breast cancer treatment. *Clin Pharmacol Ther* 2006;80(1):61-74.
2. Dezentje V, Van Blijderveen, NJ, Gelderblom, H, et al. Concomitant CYP2D6 inhibitor use and tamoxifen adherence in early-stage breast cancer: A pharmacoepidemiologic study. *J Clin Oncol* 2009;27(suppl):18s (abstr CRA509).
3. Aubert RE, Stanek EJ, Yao JR, et al. Risk of breast cancer recurrence in women initiating tamoxifen with CYP2D6 inhibitors. *J Clin Oncol* 2009;27(suppl):18s (abstr CRA508).

4. Kelly CM, Juurlink DN, Gomes T, et al. Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. *BMJ* 2010;340:c693 (published online: 8 February 2009 as doi:10.1136/bmj.c693).

DRUG UPDATE

PharmaCare Coverage for Aprepitant (EMEND®) Effective 16 March 2010, PharmaCare has started funding aprepitant under the following limited coverage special authority criteria:

- Indication: for the prevention of acute and delayed nausea and vomiting due to highly-emetogenic cancer chemotherapy in combination with a 5-HT₃ antagonist and dexamethasone.
- Approval Period/Duration: up to a maximum number of standard, planned treatment cycles of highly-emetogenic cancer chemotherapy (usually 6 or fewer treatment cycles), as specified in the relevant BC Cancer Agency chemotherapy protocol.

Highly-emetogenic chemotherapy is defined by greater than 90% of patients experiencing emesis if not premedicated with antiemetics before chemotherapy. Emetogenicity of chemotherapy is determined in accordance with the BC Cancer Agency Cancer Drug Manual for single agent chemotherapy and with the BC Cancer Agency chemotherapy protocols for combination chemotherapy (see individual protocols for assessment of emetogenicity and SCNAUSEA supportive care protocol rating). The SCNAUSEA supportive care protocol is available at: (www.bccancer.bc.ca/HPI/ChemotherapyProtocols/SupportiveCare)

Note that the coverage is not intended for the prevention of nausea and vomiting with cancer chemotherapy that has high-moderate (60-90% emesis) or low-moderate (30-60% emesis) emetogenic potential. However, exceptional case coverage requests may be submitted to PharmaCare. Exceptional case submissions are required for all patients who do not meet the above Limited Coverage criteria, from all physicians (including those with specialist exemption).

Medical oncologists, gynecologic oncologists, and general practitioners specializing in oncology (GPO's) are invited to apply for exemption from Special Authority form by completing a 1-page Collaborative Prescribing Agreement (http://www.health.gov.bc.ca/pharmacare/pdf/cpa_aprepitant.pdf).

For more details, see <http://www.health.gov.bc.ca/pharmacare/sa/criteria/restricted/aprepitant.html>.

Gefitinib (IRESSA®) for Non-Small Cell Lung Cancer (NSCLC) has recently been approved by Health Canada. Gefitinib is an oral tyrosine kinase inhibitor of the epidermal growth factor receptor (EGFR). The new indication is for the first line treatment of patients with locally advanced or metastatic NSCLC with EGFR mutations. Note that this differs from its restricted use as second line treatment for advanced or metastatic NSCLC under the IRESSA Patient Registry (IPR). Full prescribing information is available at: www.astrazeneca.ca/en/products/.

Currently, the BC Cancer Agency has no funding for gefitinib as first line treatment of NSCLC.

1. New patients: physician and patient should complete the enrollment form for the IRESSA Alliance Program (fax 1-888-891-1116). The program will coordinate coverage if patients have third party insurance or provide compassionate supply until coverage can be secured. The BCCA regional centre pharmacies are *not* involved in the dispensing of gefitinib to these patients.
2. Patients already on gefitinib under the IPR: there will be no change in any process with these patients.

For more details, contact the IRESSA Alliance Program at 1-877-754-7542 (iressa@supportprogram.com) or go to the website www.egfr-canada.ca.

CANCER DRUG MANUAL

Tamoxifen Monograph has been expanded to include information about antidepressants and their potential for interaction with tamoxifen. See Editor's Choice in this issue for more details.

BENEFIT DRUG LIST

The following treatment program has been added on the benefit drug list as a class I indication for **Anastrozole, Exemestane** and **Letrozole** effective 1 April 2010:

- hormonal treatment for advanced endometrial cancer in postmenopausal women with contraindications to tamoxifen or intolerant of tamoxifen (GOENDAI)

PROVINCIAL SYSTEMIC THERAPY POLICIES

The **Intrathecal Chemotherapy Policy (Policy III-50)** has been revised to reflect the current warning label for cytotoxic drugs which should never be given by the intrathecal route.

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
GIGECC	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	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.
GIOCTLAR	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Symptomatic Management Of Functional Carcinoid And Neuroendocrine Tumours Of The GI Tract Using Octreotide (SANDOSTATIN® LAR)
GIPE	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Palliative Therapy Of Neuroendocrine Tumours Using Cisplatin And Etoposide
GOENDAI	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Advanced Therapy for Endometrial Cancer using an Aromatase Inhibitor
HNNLAPRT	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Treatment of Locally Advanced Nasopharyngeal Cancer with Concurrent Cisplatin and Radiation
LUAJPC	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Treatment of Resected Non-Small Cell Lung Cancer with Carboplatin and Paclitaxel
LUSCTOP	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Treatment of Recurrent Small Cell Lung Cancer (SCLC) with Topotecan

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

CODE	Protocol	PPPO	Patient Handout	Changes	Protocol Title
BRAVTRAD	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<i>Protocol title clarified</i>	Palliative Therapy for Metastatic Breast Cancer using Trastuzumab (HERCEPTIN®) and Paclitaxel as First-Line Treatment for Advanced Breast Cancer
BRAVTRAP	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<i>Protocol title clarified</i>	Palliative Therapy for Metastatic Breast Cancer using Trastuzumab (HERCEPTIN®) and Docetaxel as First-Line Treatment for Advanced Breast Cancer
CNIME	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<i>Tests and Treatment sections clarified</i>	Ifosfamide, Mesna and Etoposide in the Treatment of Recurrent Brain Tumours
GICART	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<i>Capecitabine dosing schedule clarified</i>	Curative Combined Modality Therapy for Carcinoma of the Anal Canal using Mitomycin, Capecitabine and Radiation Therapy
GICPART	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<i>Capecitabine dosing schedule clarified</i>	Curative Combined Modality Therapy for Carcinoma of the Anal Canal using Cisplatin, Capecitabine and Radiation Therapy
UHCETRT	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<i>Protocol code revised to UHNLACETRT, timing of radiation clarified, contact physician revised</i>	Combined Cetuximab and Radiation Treatment for Locally Advanced Squamous Cell Carcinoma of the Head and Neck
UHNLACETRT	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<i>See UHCETRT</i>	Combined Cetuximab and Radiation Treatment for Locally Advanced Squamous Cell Carcinoma of the Head and Neck
HNLANPRT	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<i>Antiemetics clarified</i>	Treatment of Locally Advanced Nasopharyngeal Cancer with Concurrent Cisplatin and Radiation
UMYMPBOR	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<i>Frequency of bloodwork clarified</i>	Treatment of Multiple Myeloma using Melphalan, Prednisone and Weekly Bortezomib

DELETED PROTOCOLS, PPPOs AND PATIENT HANDOUTS (AFFECTED DOCUMENTS ARE CHECKED):

CODE	Protocol	PPPO	Patient Handout	Protocol Title
GIPAJFF	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Adjuvant Therapy for Resected Pancreatic Cancer using Leucovorin and Fluorouracil
HNDE	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Therapy for recurrent and metastatic nasopharyngeal cancer using Cisplatin and Etoposide

WEBSITE RESOURCES AND CONTACT INFORMATION

WEBSITE RESOURCES	www.bccancer.bc.ca
REIMBURSEMENT AND FORMS: BENEFIT DRUG LIST, CLASS II, BC CANCER AGENCY 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

CONTACT INFORMATION	www.bccancer.bc.ca	bulletin@bccancer.bc.ca
BC CANCER AGENCY	(604) 877-6000	Toll-Free 1-(800) 663-3333
PROVINCIAL SYSTEMIC THERAPY PROGRAM	Ext 2247	mclin@bccancer.bc.ca
COMMUNITIES ONCOLOGY NETWORK BUSINESS AFFAIRS.....	Ext 2744	david.leung@bccancer.bc.ca
UPDATE EDITOR	Ext 2288	mdelemos@bccancer.bc.ca
COMMUNITIES ONCOLOGY NETWORK PHARMACY EDUCATORS...	www.bccancer.bc.ca/RS/CommunitiesOncologyNetwork/Educators/Pharmacists/cap_bcca@bccancer.bc.ca
COMPASSIONATE ACCESS PROGRAM OFFICE	Ext 6277	cap_bcca@bccancer.bc.ca
DRUG INFORMATION	Fax (604) 708-2026 Ext 6275	druginfo@bccancer.bc.ca
EDUCATION RESOURCE NURSE	Ext 2638	nursinged@bccancer.bc.ca
NURSING PROFESSIONAL PRACTICE	Ext 2623	ilundie@bccancer.bc.ca
LIBRARY/CANCER INFORMATION.....	1-(888)-675-8001..... Ext 8003	requests@bccancer.bc.ca
OSCAR HELP DESK	1-(888)-355-0355..... Fax (604) 708-2051	oscar@bccancer.bc.ca
PHARMACY CHEMOTHERAPY CERTIFICATION	(250) 712-3900	rxchemocert@bccancer.bc.ca
PHARMACY PROFESSIONAL PRACTICE	Ext 686741 (250) 519.5574	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

Editorial Review Board

Mário de Lemos, PharmD, MSc (Oncol) (Editor)
 Johanna Den Duyf, MA
 Poonam Kothare (Editorial clerk)
 Judy Oliver, BScN, MEd

Beth Morrison, MLS
 Jaya Venkatesh, MHA, CMA
 Susan Walisser, BSc (Pharm)