BC Cancer Agency

Systemic Therapy Update

Volume 7, Number 3 *for health professionals who care for cancer patients* March 2004
Website access at http://www.bccancer.bc.ca/STUpdate

INSIDE THIS ISSUE

FAX request form and IN TOUCH phone list are provided if additional information is needed.

CANCER MANAGEMENT GUIDELINES

Guidelines on Androgen Ablation, Osteoporosis and Prostate Cancer Most men with prostate cancer are over 65 years of age when osteoporosis is a major health concern. Androgen ablation therapy in prostate cancer patients over prolonged periods is also a significant risk factor for inducing osteoporosis. Hence, the BCCA Genitourinary Tumour Group has developed guidelines and a patient information pamphlet on the prevention and management of osteoporosis in prostate cancer patients. The guidelines can be found on the BC Cancer Agency website under Health Professionals Info, Cancer Management Guidelines, Genitourinary, Prostate, Osteo.

The Cancer Management Guidelines are available on the BC Cancer Agency website (http://www.bccancer.bc.ca/CaMgmtGuidelines/) under Health Professionals Info, Cancer Management Guidelines.

BENEFIT DRUG LIST

The current Benefit Drug List, Class II forms and Undesignated Indication Application forms are available on the BC Cancer Agency website (http://www.bccancer.bc.ca/ChemoProtocols/Forms/) under Health Professionals Info, Chemotherapy Protocols, Frequently Used Forms.

LIST OF NEW AND REVISED PROTOCOLS

The **INDEX to BC Cancer Agency Protocol Summaries** is revised monthly (include tumour group, protocol code, indication, drugs, last revision date and version). Protocol codes for treatments requiring "Undesignated Indication" approval are prefixed with the letter **U**.

- **BRAJACT** revised (clarification of Dose Modifications for ANC): Adjuvant therapy for breast cancer using doxorubicin and cyclophosphamide followed by paclitaxel (Taxol ®)
- **(U)BRAJCAF** revised (protocol changed to undesignated request only): Adjuvant therapy for breast cancer using cyclophosphamide, doxorubicin and fluorouracil
- **GOENDCAD** revised (typo corrected in Dosing Modifications): Treatment of primary advanced or recurrent endometrial cancer using carboplatin and docetaxel

- **LYCVPPABO** revised (reference added): Treatment of Hodgkin's disease with cyclophosphamide, vinblastine, procarbazine and prednisone

Protocols are available on the BC Cancer Agency website (http://www.bccancer.bc.ca/ChemoProtocols/) under Health Professionals Info, Chemotherapy Protocols.

PRE-PRINTED ORDER UPDATE

Pre-printed orders should always be checked with the most current BC Cancer Agency protocol summaries. The BC Cancer Agency Vancouver Centre has prepared chemotherapy pre-printed orders, which can be used as a guide for reference. An index to the orders can be obtained by Fax-back.

- **UGOOVCAGE** new: Treatment of advanced ovarian cancer in patients who have progressed or recurred following first-line platinum-based treatment using carboplatin and gemcitabine

PATIENT EDUCATION

Osteoporosis in Prostate Cancer Patients The BCCA Genitourinary Tumour Group has developed guidelines and a patient information pamphlet on prevention and management of osteoporosis in prostate cancer patients. See the Cancer Management Guidelines section in this issue for more details.

Patient information handouts for cancer drugs are available on the BC Cancer Agency website (www.bccancer.bc.ca/DrugDatabasePt/) under Health Professionals Info, Cancer Drug Manual, Drug Information for the Patient. For treatment protocol specific information, go to the BC Cancer Agency website (www.bccancer.bc.ca) under Health Professionals Info, Chemotherapy Protocols, Information for the Patient.

CANCER DRUG MANUAL

The Cancer Drug Manual is available on the BC Cancer Agency website www.bccancer.bc.ca/cdm/.

FOCUS ARTICLES

Health Canada Special Access Programme

The Health Canada Special Access Program (SAP) provides Canadians with the opportunity to be treated with drugs that are not approved for sale in Canada. These drugs are exempt from all provisions of the Food and Drugs Act and Regulations and therefore it is the prescribing physician who is professionally responsible for all aspects of the use of the drug. SAP drugs are both patient specific and physician specific.

Obtaining SAP drugs can be challenging. Each SAP drug has unique requirements but typically there are three different forms completed and faxed to three different locations:

- BCCA undesignated form or a class 2 form completed by the physician and faxed to the Provincial Pharmacy at 604-708-2026.
- Health Canada Special Access Request (SAR) form completed by physicians and pharmacists and faxed to Health Canada at 613-941-3194. Please note that a pharmacist may submit the SAR form for *reorders*.
- Company specific forms completed by physician and pharmacist and faxed to the manufacturer of the drug.

A chart for drugs with special ordering procedures (eg, SAP drugs, gefitinib [Iressa®]) has been developed and is accessible from the BC Cancer Agency website (http://www.bccancer.bc.ca/ChemoProtocols/Forms/) under Health Professionals Info, Chemotherapy Protocols, Frequently Used Forms. CON centres can also get additional guidance on SAP applications from their Regional Cancer Centre Pharmacy.

Submitted by
Linda Hamata, BSc(Pharm)
Staff Pharmacist,
Vancouver Centre – BC Cancer Agency

Enhanced Vincristine Neurotoxicity by Itraconazole – A BCCA Case Report and Review of Literature

Vincristine is a vinca alkaloid commonly used in acute lymphocytic leukemia (ALL), Ewing's sarcoma and other types of tumours. One common side effect of vincristine is neurotoxicity, of which the most frequent manifestation is peripheral neuropathy, followed by cranial nerve neuropathy, and autonomic neuropathy. Other central neurotoxicities include headache, malaise, dizziness, seizures, mental depression, psychosis and syndrome of inappropriate antidiuretic hormone (SIADH).[1] The metabolic route of vincristine has not been clearly determined. However, vincristine appears to be extensively metabolized, probably in the liver by the cytochrome P450 microsomal enzyme system (CYP).[2]

Itraconazole is a triazole derivative often used to treat aspergillosis, blastomycosis and other kinds of fungal infections. It is a potent CYP 3A4 isoenzyme system inhibitor and may increase plasma concentrations of drugs metabolized by this pathway.[3] At the BC Cancer Agency Vancouver Center, a 38-year old woman with pre-B cell ALL experienced neurotoxicities, possibly induced by an interaction between vincristine and itraconazole. The patient was diagnosed with ALL in 2002 and had received two complete courses of consolidation chemotherapy. As part of the protocol, she received vincristine 2 mg on days 1, 8, 15, and 22 per cycle. During both cycles of chemotherapy, she experienced paresthesias and weakness in her handgrip likely secondary to vincristine. The patient's symptoms were resolved after a few months. On April 11, 2003, the patient went on to receive a third cycle of consolidation with vincristine. In the mean time, she was diagnosed with presumed pulmonary aspergillosis and started on itraconazole 200 mg PO bid. After two weeks out of four weekly vincristine injections, she complained of tingling of her hands. She was admitted to the BC Cancer Agency with a chief complaint of constipation and severe abdominal cramping. No further doses of vincristine were given. On April 29, 2003, she was unable to stand up even with the assistance of a walker or move her legs, but was able to move her hand and feed herself.

A MEDLINE search showed that most reports of vincristine neurotoxicity were associated with drug interactions. A 5-year-old child with ALL developed bilateral cranial nerve palsies, severe peripheral neuropathy involving upper and lower extremities, seizures, hypertension, heart failure, and SIADH after being treated with vincristine, nifedipine, and itraconazole.[4] Eight children with ALL and non-Hodgkin's lymphoma were started on weekly vincristine treatments for four weeks. Itraconazole was commenced as antifungal prophylaxis. Within two to four weeks, enhanced vincristine neurotoxicity was noted in all patients, particularly abdominal cramps and constipation.[5] In four of 14 patients with ALL who received induction chemotherapy containing weekly injections of vincristine and simultaneous antifungal prophylaxis with itraconazole, unusually severe and early vincristine-induced neurotoxicity was observed. In these patients (three female, one male), paresthesia and muscle weakness of the upper/lower extremities and paralytic ileus occurred after the first or second vincristine injection. The neurotoxic complications were more serious than those seen in a previous series of 460 ALL patients under the identical cytostatic regimen but without itraconazole prophylaxis.[6]

The underlying mechanism of the vincristine-itraconazole interaction is unknown. However, vincristine appears extensively metabolized involving CYP 3A, while itraconazole is a CYP 3A4 inhibitor. The proposed mechanism is most likely attributed to either inhibition of CYP 3A4 enzymes or blockade of P-glycoprotein pumps. These interactions are clinically significant and can lead to severe vincristine toxicity if the symptoms are not detected early.[7] Upon , In a study with 11 cases of itraconazole-enhanced vincristine toxicity, cessation of itraconazole led to complete resolution of symptoms in 10 of 11 patients.[8]

Our patient was transferred to a rehabilitation facility on May 26, 2003. Her motor power improved significantly in the following three weeks. She had been walking with a walker. In June 2003, she received a fourth cycle of ALL consolidation chemotherapy. This chemo cycle had been modified to eliminate vincristine. By October 2003, she regained normal motor power in all four extremities. She is currently on maintenance chemotherapy with daily 6-mercaptopurine and weekly methotrexate.

In conclusion, most of the reported cases of vincristine neurotoxicity involve patients with ALL, treated with weekly injections of vincristine, who also received itraconazole as fungal prophylaxis. Our patient received vincristine as ALL consolidation and itraconazole as treatment for presumed pulmonary aspergillosis. **It is recommended that concurrent administration of vincristine and itraconazole should be avoided whenever possible. If these agents must be given concomitantly, closely monitor the patient for vincristine toxicity. It may be necessary to discontinue the itraconazole.**

Rongrong Karim, BSc(Pharm)
Staff Pharmacist,
Vancouver Centre – BC Cancer Agency

Reference:

1. BC Cancer drug manual, www.bccancer.bc.ca. Accessed Dec 15, 2003.
2. American Hospital Formulary System Drug Information 2002. 1171-1174.
3. Mosby drug consult, www.mdconsult.com. Accessed Dec 16, 2003.
4. Sathiapalan RK, El-Solh H. Enhanced vincristine neurotoxicity from drug interactions: case report and review of literature. Pediatric Hematology & Oncology 2001;18 (8):543-6.
5. Kamaluddin M, McNally P, Breatnach F, O'Marcaigh A, Webb D, O'Dell E, Scanlon P, Butler K, O'Meara A. Potentiation of vincristine toxicity by itraconazole in children with lymphoid malignancies. Acta Paedictrica 2001;90 (10):1204-7.
6. Bohme A, Ganser A, Hoelzer D. Aggravation of vincristine-induced neurotoxicity by itraconazole in the treatment of adult ALL. Annals of Hematology 1995;71(6):311-2.
7. Chan JD. Pharmacokinetic drug interactions of vinca alkaloids: summary of case reports. Pharmacotherapy 1998; 18 (6): 1304-7.
8. Jeng MR, Feusner J. Itraconazole-enhanced vincristine neurotoxicity in a child with acute lymphoblastic leukemia. Pediatric Hematology & Oncology 2001;18 (2):137-42.

PROVINCIAL SYSTEMIC THERAPY PROGRAM POLICIES

BC Cancer Agency Systemic Therapy Policies are available on the BC Cancer Agency website (http://www.bccancer.bc.ca/ChemoProtocols/Policies/) under Health Professionals Info, Chemotherapy Protocols, Policies and Procedures.

LIBRARY/CANCER INFORMATION CENTRE

Unconventional Cancer Therapies Manual is available on the BC Cancer Agency website www.bccancer.bc.ca under Patient/Public Info, Unconventional Therapies. The manual consists of 46 short

monographs on the more commonly used unconventional cancer therapies (e.g., Essiac, vitamins, teas, shark cartilage) and includes tips for the patient and family on how unconventional therapies can be evaluated. For each therapy the manual provides proponent/advocate claims, as well as evidence-based evaluation/critique quotations from the literature.

This manual is currently being revised and the Fourth Edition will be published in the near future.

IN TOUCH	www.bccancer.bc.ca	bulletin@bccancer.bc.ca
BC Cancer Agency	(604)-877-6000	Toll-Free 1-(800)-663-3333
Communities Oncology Network	Ext 2744	jvenkate@bccancer.bc.ca
Education Resource Nurse	Ext 2638	nursinged@bccancer.bc.ca
Nursing Professional Practice	Ext 2623	ilundie@bccancer.bc.ca
Pharmacy Professional Practice	Ext 2247	gconcon@bccancer.bc.ca
Provincial Systemic Therapy Program	Ext 2247	gconcon@bccancer.bc.ca
Communities Oncology Network Pharmacist	Ext 6277	francish@bccancer.bc.ca
Drug Information	Ext 6275	druginfo@bccancer.bc.ca
Library / Cancer Information	Ext 2690	bethm@bccancer.bc.ca
Update Editor	Ext 2288	mdelemos@bccancer.bc.ca
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

BC CANCER AGENCY SYSTEMIC THERAPY UPDATE REQUEST FORM

FAX (604) 877-0585
bulletin@bccancer.bc.ca

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UPDATES **Please ☑ Fax-Back information below:**

Most items have been hyperlinked for easy access

☐ All items for **March 2004 (Vol 7 №3)**			
Cancer Drug Manual Monographs: (also available on our website www.bccancer.bc.ca)			
Patient Education Handout: (also available on our website www.bccancer.bc.ca)			
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Reimbursement (also available on our website www.bccancer.bc.ca)			
☐ Benefit Drug List (01 January 2004)			
☐ Class 2 Form (01 January 2004)			
Systemic Therapy Update Index (also available on our website www.bccancer.bc.ca)			
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