BC Cancer Agency

Systemic Therapy Update

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Website access at http://www.bccancer.bc.ca/STUpdate/

INSIDE THIS ISSUE

EDITOR'S CHOICE

FOCUS ON BEVACIZUMAB (AVASTIN®): A NOVO ACTING AGENT FOR COLORECTAL CANCER

Bevacizumab (Avastin®), a novo acting antiangiogenic agent made by Genentech Inc., is approved in the US for first-line treatment of metastatic colon or rectal carcinoma, in combination with IV 5-fluorouracil based treatment. Two randomised clinical trials showed that the addition of bevacizumab to a regimen of either 5-fluorouracil (5-FU) plus leucovorin or 5-FU plus leucovorin combined with irinotecan significantly improved response rate and time to progression and increased overall survival.

Bevacizumab is dosed at 5 mg/kg every 14 days and may be continued until disease progression. The dose should be diluted in 100 mL NS and has an 8-hour stability when stored at 2-8°C. The first dose should be administered by IV over 90 minutes. If this first dose is well tolerated, the second dose is given over 60 minutes. If the second dose is well tolerated, subsequent doses may be given over 30 minutes (5).

As bevacizumab is not available in Canada, patients who wish to be treated with this drug must purchase it individually at their own expense in the US and obtain approval via the Undesignated application process (for more information visit the website at www.bccancer.bc.ca/HPI/ChemotherapyProtocols/Forms.htm). Pharmacists and nurses should consult their colleges of practice (eg, BC College of Pharmacists, RNABC) and practice institutions regarding the use of a drug without notice of compliance.

Pharmacology

Bevacizumab, a humanized monoclonal antibody, represents a new class of antiangiogenic agents. In the past, research has focused on cancer cells and the development of therapies that target these cells. However, over the last 10-15 years, research has indicated that tumours are complex tissues made up of a variety of cells, which are all potential targets for cancer therapy (1). Endothelial cells are included in that complex tissue and these cells play a role in angiogenesis and the mechanism of action of bevacizumab.

Angiogenesis is the development of new blood vessels, which is necessary for tumour growth, invasion and metastasis. Without new blood vessels, tumours are limited in their ability to grow (2). A central mediator of angiogenesis is a heparin-binding glycoprotein called "vascular endothelial growth factor" (VEGF) (2,3). VEGF has a high affinity for endothelial cells and although expressed in many cells, VEGF has increased expression in tumour cells. Overexpression of VEGF is often correlated with a poor prognosis in numerous malignancies,

including colon cancer, NSCLC, ovarian and breast cancer, AML and hepato-cellular carcinoma (2). VEGF acts directly through activation, proliferation, migration and survival of endothelial cells (3). VEGF stimulates growth and survival of immature vasculature. Interestingly, normal angiogenesis is ordered and highly regulated; however angiogenesis of immature tumour vasculature is chaotic and irregular, producing blood vessels that are structurally and functionally abnormal. This may impact on delivery of oxygen and nutrients to the tumour, as well as chemotherapy. VEGF also modulates immune cell function by decreasing the host's ability to eradicate tumour cells (3). Theoretically, the inhibition of VEGF has the potential to prevent new growth of tumour vasculature, cause vasculature regression, improve anti-tumour immune response and possibly stabilize tumour vasculature, therefore, increasing delivery of traditional chemotherapy (2,3,4). At present, greater understanding of the differences between normal and tumour vasculature is being researched.

Bevacizumab binds to VEGF and prevents the interaction of VEGF to its receptors on the surface of endothelial cells (5). Bevacizumab, therefore, inhibits numerous activities of VEGF, including endothelial cell growth, angiogenesis, and immune response. VEGF has several isoforms, with VEGF-A most highly associated with mediation of angiogenesis. Bevacizumab binds all VEGF isoforms with high affinity (2).

The estimated half-life of Bevacizumab is 20 days, with a range of 11 to 50 days. The metabolism and elimination mechanism of bevacizumab has yet to be reported in the literature. Clearance of bevacizumab varies by body weight, gender and tumour burden (5).

Adverse effects

In clinical trials, the most serious adverse events associated with bevacizumab were GI perforation, wound healing complication, hemorrhage, arterial thromboembolic events, hypertensive crisis, nephrotic syndrome and congestive heart failure (2,4,5,6). Grade 1 epistaxis was the most common hemorrhage, but life threatening and fatal pulmonary hemorrhage also occurred.

Other adverse effects include asthenia, pain, hypertension, diarrhea, leucopenia, abdominal pain, headache, nausea, vomiting, anorexia, stomatitis, constipation, upper respiratory infection, dyspnea, exfoliative dermatitis and proteinuria (4,5,6).

To date, infusion reactions with first dose bevacizumab are uncommon and severe reactions rare. Bevacizumab infusions should be interrupted in any patient experiencing a severe infusion reaction. Information on re-challenge is currently not available (5,6).

It is recommended that bevacizumab not be used within 28 days of surgery, as this may impair wound healing. Likewise, the preoperative use of Bevacizumab must be undertaken with caution. No specific time recommendations exist, but the estimated half- life of 20 days should be taken into consideration when planning surgery (4,5).

Drug interactions

No formal drug interaction studies with anti-neoplastic agents have been done to date. In one study where patients received irinotecan/5-FU/leucovorin (bolus 5-FU) with or without bevacizumab, the active metabolite of irinotecan, SN38, was on average 33% higher in patients on the bevacizumab arm, even though the irinotecan concentrations were similar in both groups. This group of patients did experience a higher incidence of grade 3-4 diarrhea and neutropenia (1). However, further trials are required to elaborate on this finding, due to the small sample size and high inter-patient variability of this one particular trial. Theoretically, it would seem prudent to use bevacizumab cautiously with other medications that increase the risk of bleeding (e.g., NSAIDs, ASA, warfarin) (2,4) and most of the clinical trials to date have specifically excluded patients taking these agents.

Use in other malignancies

As of March 15, 2005, Roche and Genentech Inc. announced that bevacizumab significantly improves survival in patients with advanced NSCLC (7) based on the preliminary results of a Phase II/III trial. This study randomized 878 patients with advanced, non-squamous NSCLC to treatment with paclitaxel and carboplatin with or without bevacizumab 15 mg/kg. Treatment was given every 3 weeks, for up to six courses. Details of the study are to be presented at ASCO in May 2005 (7).

Ongoing trials of Bevacizumab in epithelial malignancies include Phase II studies in refractory ovarian cancer and Phase III trials in adjuvant colorectal carcinoma, metastatic breast cancer, pancreatic cancer and renal cell carcinoma.(8,10).

Angiogenesis also plays a role in hematological malignancies (2), enhancing the survival of hematopoietic stem cells and leukemic cells, and facilitating recruitment of hematopoietic stem cells to sites of angiogenesis. Bevacizumab use in hematologic malignancies is being explored in acute myeloid leukemia, chronic myeloid leukemia, multiple myeloma and non-Hodgkin's lymphoma (2,9).

References:

1. RJ Ignoffo. Targeting vascular endothelial growth factor: a novel approach in the treatment of cancer. Am J Health-Syst Pharm. 2004;61(Suppl 5) S3.
2. Zondor SD, Medina PJ. Bevacizumab: an angiogenesis inhibitor with efficacy in colorectal and other malignancies. Ann Pharmacother. 2004;38:1258-64.
3. EK Bergsland. Vascular endothelial growth factor as a therapeutic target in cancer. Am J Health-Syst Pharm. 2004;61(Suppl 5) S12-20.
4. RJ Ignoffo. Overview of bevacizumab: a new cancer therapeutic strategy targeting vascular endothelial growth factor. Am J Health-Syst-Pharm. 2004;61(Suppl 5) S21-26.
5. Avastin® (bevacizumab) product monograph, Genentech BioOncology, April 2004.
6. www.avastin.com/avastin/nurseFaqPro.m accessed 15 March 2005.
7. www.roche.com/med-cor-2005-03-15 accessed 15 March 2005.
8. www.roche.com/home/investors/inv_pipeline accessed 31 March 2005.
9. EK Bergsland. Update on clinical trials targeting vascular endothelial growth factor in cancer. Am J Health-Syst Pharm. 2004; 61(Suppl 5) S12-20.
10. www.gene.com/pipeline/status/oncology/avastin/index.jsp accessed 31 March 2005.

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CANCER DRUG MANUAL

Paclitaxel Monograph has recently been revised to reflect additional information on premedications and infusion time when the drug is given weekly in lower doses:

- Lower doses of paclitaxel – 80 mg/m^2 (range 50-90 mg) – have been safely given when infused over 1 hour. Preliminary data suggest that less premedication may be needed with weekly dosing of lower doses of paclitaxel (50-90 mg/m^2/week). This involves premedications given 30 minutes before the first weekly dose of paclitaxel with: dexamethasone 10 mg IV, diphenhydramine 25 mg IV, and an H_2-antagonist (e.g., cimetidine 300 mg IV, ranitidine 50 mg IV).

- If no hypersensitivity reactions occur, no premedications may be needed for subsequent weekly paclitaxel doses. If hypersensitivity reactions occur, paclitaxel is delayed for 24 hours before re-challenge. Premedications for re-challenge include dexamethasone 20 mg PO given 12 and 6 hours before treatment, plus IV premedications given 30 minutes before paclitaxel: dexamethasone 10 mg, diphenhydramine 25 mg and H_2-antagonist (e.g., cimetidine 300 mg, ranitidine 50 mg). If no hypersensitivity reactions occur, standard premedications (see above) will be used for subsequent paclitaxel doses.

Revised Patient Handouts on Cancer Drugs The patient information handouts for drugs, which are used for lymphomas and haematological malignancies, have undergone minor revisions to better reflect their use to control leukemias of either lymphoid or myeloid origins. The following drugs have been revised:

- busulfan (oral and injectable)
- chlorambucil
- daunorubicin
- hydroxyurea
- mercaptopurine
- thioguanine

PATIENT EDUCATION

Revised Patient Handouts on Cancer Drugs The patient information handouts for drugs which are mainly used for lymphomas and haematological malignancies have been revised. See under Cancer Drug Manual for more details.

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**.

- **LKANAG** revised (eligibility clarified): Anagrelide as second-line treatment of thrombocytosis related to myeloproliferative disorders
- **LUMMPPEM** revised (clarified dose modification in renal dysfunction for pemetrexed)) : Treatment of malignant mesothelioma with platinum and pemetrexed (ALIMTA®)
- **(U)MYBORTEZ** revised (requirement for Health Canada Special Access Programme deleted, dose adjustment for peripheral neuropathy added): Treatment of multiple myeloma with bortezomib
- **SCEPO** revised (algorithm clarified to be consistent with the text): Guidelines for selecting and monitoring oncology patients for epoetin alfa (erythropoietin) therapy

LIST OF NEW AND REVISED PRE-PRINTED ORDERS

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

- **LYGDP** revised (class II indication added): Treatment of Lymphoma with Gemcitabine, Dexamethasone and Cisplatin (GDP)
- **(U)MYBORTEZ** revised (requirement for Health Canada Special Access Programme deleted, dose adjustment for peripheral neuropathy added): Treatment of multiple myeloma with bortezomib

CONTINUING EDUCATION – MARK YOUR CALENDAR

- **2-5 October 2005**: Annual Canadian Association of Oncology Nursing Conference, Moncton, New Brunswick (www.cos.ca/cano)
- **23-26 October 2005**: 1st International Cancer Control Congress, Pan Pacific Hotel, Vancouver, BC (www.cancercontrol.org)
- **28-30 October 2005**: National Oncology Pharmacy Symposium, Sheraton Wall Centre, Vancouver, BC (http://capho.ca/)
- **3-5 November 2005**: BCCA Annual Cancer Conference, Westin Bayshore 1601 Bayshore Drive, Vancouver, BC

WEBSITE RESOURCES

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

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

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

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

The Cancer Chemotherapy Pre-Printed Orders are available on the BC Cancer Agency website (www.bccancer.bc.ca/ChemoProtocols) under Health Professionals Info, Chemotherapy Protocols. Pre-Printed Orders are posted at the index page of each tumour site.

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

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

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	(604)-675-8003	requests@bccancer.bc.ca
OSCAR Hotline	1-888-355-0355	
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
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UPDATES **Please ☑ Fax-Back information below**:

Most items have been hyperlinked for easy access

☐All items for **May 2005 (Vol 8 № 5)**					
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)					
☐ busulfan	☐ chlorambucil	☐ daunorubicin	☐ hydroxyurea	☐mercaptopurine	☐ thioguanine
Protocol Summaries: (also available on our website www.bccancer.bc.ca)				Index of Protocol Summaries	
☐ LKANAG	☐ UMYBORTEZ	☐ SCEPO	☐ LUMMPPEM		
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☐ LYGDP					
☐ UMYBORTEZ					
Provincial Systemic Therapy Program Policies					
Reimbursement (also available on our website www.bccancer.bc.ca)					
☐ Benefit Drug List (01 March 2005)		☐ Class 2 Form (01 March 2005)			
Systemic Therapy Update Index (also available on our website www.bccancer.bc.ca)					
☐ Jan-Dec 2000	☐ Jan-Dec 2001	☐ Jan-Dec 2002	☐ Jan-Dec 2003		
☐ Jan-Dec 2004					