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

COMPASSIONATE ACCESS TO MAINTENANCE RITUXIMAB THERAPY

Rituximab Maintenance Therapy The BC Cancer Agency Lymphoma Tumour Group has developed guidelines on the compassionate access to maintenance rituximab therapy (ULYRMTN) for patients with indolent lymphomas:

1. Currently receiving primary chemotherapy with LYCVPR protocol,
2. Completed primary chemotherapy with LYCVPR protocol within the six months preceding adoption of these guidelines, therefore on or after 1 September 2005,
3. Currently receiving chemotherapy for relapsed indolent lymphoma, with or without rituximab included in the chemotherapy regimen,
4. Completed chemotherapy for relapsed indolent lymphoma, with or without rituximab included in the chemotherapy regimen, within the six months preceding adoption of these guidelines, therefore on or after 1 September 2005.

Use of rituximab maintenance for these indications requires ***undesignated request and approval***.

These guidelines are based on data reported at the American Society of Hematology (ASH) annual meeting in December 2005, showing that maintenance rituximab can improve the survival of patients with indolent B-cell lymphoma who have responded to chemotherapy. This includes favourable impact on progression free survival and more moderate but still discernible impact on overall survival. These benefits are present even when such patients have received rituximab as part of their preceding chemotherapy regimen (*Hochster, ASH 2005, abstract 349; Van Oers, ASH 2005, abstract 353; Hiddemann, ASH 2005, abstract 920*).

Currently, there is no evidence of superiority of one versus another schedule and dose. Hence, the Lymphoma Tumour Group has adopted the most convenient and least costly regimen as described by Van Oers:

- rituximab 375 mg/m^2 once every 3 months for 2 years, provided the lymphoma does not progress during that time.

FOCUS ON BEVACIZUMAB

Bevacizumab (Avastin®) is a vascular endothelial growth factor inhibitor that was reviewed in detail in the May 2005 issue of the Systemic Therapy Update. Since then, it has received the Notice of Compliance from Health Canada for first- and second-line treatment of metastatic colorectal cancer in combination with chemotherapy based on randomized trials showing a survival advantage in these settings.[1,2] Bevacizumab is now commercially available and is no longer available through the Health Canada Special Access Programme.

Use of bevacizumab

Undesignated requests for the addition of bevacizumab to first- or second-line chemotherapy for metastatic colorectal cancer are currently assessed at the BC Cancer Agency on a case-by-case basis. At the moment, the agency's Priorities and Evaluations Committee (PEC) is evaluating a proposal for:

- first-line chemotherapy plus bevacizumab,
- second-line chemotherapy with bevacizumab for those who have already completed first line therapy before bevacizumab became available.

The dose and frequency of bevacizumab varies depending on the accompanying chemotherapy.[1-3] Patients should have blood pressure measured prior to each dose and their urine dipped for protein. Guidelines for holding the drug in the presence of proteinuria are outlined in the protocols. Protocols and pre-printed orders are available in the gastrointestinal chemotherapy section on the website for the addition of bevacizumab to the following chemotherapy regimens:

Chemotherapy regimen	BC Cancer Agency Protocol
▪ FOLFOX	▪ UGIFFOXB
▪ FOLFIRI	▪ UGIFFIRB
▪ CAPOX	▪ UGICOXB
▪ CAPIRI	▪ UGICIRB

Serious adverse events

The Cancer Drug Manual staff is currently compiling a drug monograph for bevacizumab, which should be available on the website in April 2006. The ***serious adverse events*** encountered with this drug in clinical trials to date are:

Adverse events	Comments
arterial thrombotic events ▪ including stroke, hemorrhage, transient ischemic attacks, myocardial infarction	▪ 4.5 % overall incidence (*vs*. 2% in non-bevacizumab arms) ▪ 18% incidence in trial subjects 65 years and older who had had a prior event ▪ no increased risk of venous thromboembolic events
hypertension	▪ about 21% incidence for all grades ▪ 12% for grade 3/4, but well managed with antihypertensives; ▪
proteinuria	▪ about a 23% incidence for all grades ▪ < 1% for grade 3/4
risk of wound dehiscence, delayed/impaired wound healing, and bleeding following major surgery	insertion of central venous access devices within 48 hours of starting bevacizumab did not increase the risk of bleeding or wound healing at these sites

Patients with recent surgery, significant risk of bowel obstruction or perforation should not receive bevacizumab. Caution should be exercised in patients with significant risk factors for vascular thrombotic complications such as listed above.

The adjuvant 3 arm trial (GITAVANT) of FOLFOX, FOLFOX plus bevacizumab, or CAPOX plus bevacizumab was temporarily held as of 15 February, 2006 by the sponsor for a planned period of two months. The reasons stated are due to an accrual rate in January far exceeding expectation and a desire for patients to be followed for the first 60 days for safety end points. There are no new toxicity concerns; however the sponsor wishes to exercise caution given that this is an adjuvant trial. To date there have been 4 deaths each in the first two arms, and 7 in the CAPOX/bevacizumab arm with over 1200 enrolled patients.

A **prospective study** of serious adverse effects and quality of life is planned and being spearheaded by Drs. Barbara Melosky and Suzanne Taylor. The plan is for mandatory reporting of reason(s) for discontinuing bevacizumab and of any thrombotic, cardiac, gastrointestinal perforation, obstruction, or bleeding complications while on treatment with bevacizumab. The aim is to compile the serious side effect profile of this drug in colorectal cancer in BC, and to analyze its economic usefulness. More details will follow soon.

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References:

1. Kabbinavar F, Hurwitz HI, Fehrenbacher L, et al. Phase II Randomized trial comparing bevacizumab plus fluorouracil leucovorin with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol 2003;21:60-5.
2. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-42.
3. Giantonio BJ, Catalano PJ, Meropol NJ, et al. High-dose bevacizumab improves survival when combined with FOLFOX4 in previously treated advanced colorectal cancer: Results from the Eastern Cooperative Oncology Group (ECOG) study E3200. J Clin Oncol (Meeting Abstracts) 2005 23 (abstract 2).

CANCER DRUG MANUAL

Interferon Monograph and Handout These have been completely revised and updated. With the removal of interferon alfa-2a (Roferon®) from the Canadian market, all Cancer Drug Manual information is now specific to interferon alfa-2b (Intron-A®). As before, there are separate patient handouts for parenteral and intravesical use.

Parenteral interferon commonly causes flu-like symptoms, and up to 98% of patients experience fever. Consequently, patient instructions for the management of fever are slightly different from usual. Patients are instructed to call their doctor if they have fever *plus* another sign of infection; e.g., cough, dysuria.

An important drug interaction has been added to the monograph and handouts. Concurrent use of interferon and the herbal remedy Sho-saiko-to increases the risk of interstitial pneumonitis. This interaction came to light after the Japanese national health insurance program approved the use of Sho-saiko-to for hepatitis, a common indication for interferon. Many patients used both agents simultaneously, and several fatalities resulted. Sho-saiko-to is also known by its Chinese name, Xiao Chai Hu Tang. It is a mixture of seven ingredients: Bupleurum root, Pinellia tuber, Scutellaria root, ginseng, jujube, licorice, and ginger.

Limited Revisions of Clodronate and Docetaxel Monographs A new brand of oral and parenteral **clodronate**, Clasteon®, has been added to the monograph and handout. This has the same dosing and pharmaceutical information as the existing brands, Bonefos® and Ostac®.

Additional information has been added to the **docetaxel** monograph on dexamethasone dosing for premedication. Recent introduction of weekly docetaxel regimen has led to the use of lower doses of oral dexamethasone as premedications. There are two regimens:

- 8 mg as a single dose 1 hour prior to docetaxel administration. (BC Cancer Agency standard),
- 8 mg for 3 doses starting the night before, morning of and evening after treatment (total dose, 24 mg/week) (as used in clinical trials).

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
GIRLACF	Pre-operative combined modality therapy with radiation and capecitabine and post operative chemotherapy using fluorouracil, folinic acid (leucovorin) for locally advanced (borderline resectable or unresectable) and low rectal adenocarcinoma.
ULYRMTN	Maintenance rituximab for indolent lymphoma

Revised protocols:

The contact information has been updated on all ***Gastrointestinal*** protocols.

Code	Changes	Protocol Name
CNTAMCAR	*liver function tests clarified*	Second and third line treatment of recurrent gliomas with carboplatin and high dose tamoxifen
GIEFUP	*contact physician, typo in creatinine clearance table)*	Combined modality therapy for locally advanced esophageal cancer using cisplatin, infusional fluorouracil and radiation therapy
GIENDO1	*premeds, renal dosing, contact physician revised*	Palliative therapy of pancreatic endocrine tumors using carmustine and fluorouracil
GIFOLFIRI	*contact physician revised*	Palliative combination chemotherapy for metastatic colorectal cancer using irinotecan, fluorouracil and folinic acid (leucovorin)
GIIR	*title, eligibility, contact physician revised; typos in exclusion criteria and atropine dose corrected*	Palliative chemotherapy for metastatic colorectal cancer using irinotecan
UGIIRFUFA	*contact physician, typos in exclusion criteria and atropine dose*	Palliative combination chemotherapy for metastatic colorectal cancer using irinotecan, fluorouracil and folinic acid (leucovorin)
GIIRINALT	*title, eligibility, contact physician revised; typos in exclusion criteria corrected*	Palliative chemotherapy for metastatic colorectal cancer using weekly irinotecan
LUAJCAT	*pre-med and hypersensitivity management for paclitaxel clarified*	Adjuvant carboplatin and paclitaxel following resection of stage I, II and IIIA non-small cell lung cancer

Code	Changes	Protocol Name
LYCCOP	*deleted*	Treatment of Hodgkin's disease using cyclophosphamide, vincristine, prednisone
LYRITB	*Undesignated requirement replaced by class II*	Palliative therapy for lymphoma using radioimmunotherapy: tositumomab-priming for I^{131} tositumomab (Bexxar) *(Note: only reimbursable when prescribed by the BC Cancer Agency radiation oncologists)*
LYRITZ	*Undesignated requirement replaced by class II*	Palliative therapy for lymphoma using radioimmunotherapy: rituximab-priming for ibritumomab ^{90}Y (Zevalin) *(Note: only reimbursable when prescribed by the BC Cancer Agency radiation oncologists)*

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
GIRLACF	Capecitabine with concurrent radiation for pre-operative therapy of rectal cancer to replace fluorouracil infusion
ULYRMTN	Maintenance rituximab for indolent lymphoma
LYRITB	Palliative therapy for lymphoma using radioimmunotherapy: tositumomab-priming for I^{131} tositumomab (Bexxar)
LYRITZ	Palliative therapy for lymphoma using radioimmunotherapy: rituximab-priming for ibritumomab ^{90}Y (Zevalin)

Revised pre-printed orders:

Code	*Changes*	Protocol Name
BRAVNAV	*Identify peripheral IV only*	Palliative therapy for symptomatic metastatic breast cancer using Vinorelbine (Navelbine®)
BRAVTRNAV	*Identify peripheral IV only*	Palliative therapy for metastatic breast cancer using trastuzumab (Herceptin®) and vinorelbine
CNCARV	*Clarification of Return Appointment Orders for CBC & Diff, Platelets on Day 14 or 21 as outlined in the protocol*	Carboplatin and etoposide in the treatment of recurrent ependymoma
CNTAM	*Tamoxifen treatment option clarified*	Tamoxifen for patients with recurrent brain tumors which are resistant to first line chemotherapy
GIENDO1	*Added Creatinine Clearance to treatment parameters. Premeds changed to refer to SCNAUSEA protocol recommendations. The need to use PVC equipment added to the chemotherapy portion.*	Palliative therapy of pancreatic endocrine tumors using carmustine and fluorouracil
GIIRINALT	*Deleted instructions for RN to assess for stomatitis and diarrhea. Standing Order - added " or CON" to the BCCA Pharmacy portion.*	Palliative chemotherapy for metastatic colorectal cancer using weekly irinotecan
GOOVVIN	*Day 8 labs are not necessary*	Palliative Chemotherapy for Re-treatment of Ovarian, Tubal, and Peritoneal Cancer Using Vinorelbine

Revised pre-printed orders:

Code	*Changes*	Protocol Name
LYFLUDR	*added creatinine to the "may proceed with" section; Added two notes: (1) re calculated creatinine clearance and (2) regarding dose modification and added creatinine to the tests section.*	Treatment of Chronic Lymphocytic Leukemia or Prolymphocytic Leukemia with Fludarabine and Rituximab
UMYBORTEZ	*added AST, serum bilirubin, alkaline phosphatase to tests section and to the "may proceed with" section*	Treatment of Multiple Myeloma with Bortezomib

PROVINCIAL SYSTEMIC THERAPY PROGRAM POLICIES

Physician Coverage for Medical Emergencies During Delivery of Selected Chemotherapy Drugs

This patient care policy (III-60) has been completely updated with additional information on new drugs and a general description of the potential hypersensitivity reactions, onset and incidence.

Drugs introduced into clinical use since the original policy in 2001 were reviewed for their propensity to cause hypersensitivity reactions. The main data source came from the manufacturer's product monographs and a MEDLINE search. The threshold for inclusion in the final policy was largely based on the emphasis placed by the manufacturer, although the literature report may also be pivotal. The length of physician coverage takes into account of the likely documented onset of reactions and the usual infusion time. For example, oxaliplatin is usually infused over 2 hours. Although the onset of hypersensitivity reactions within 30 minutes after the start of oxaliplatin, [1-7] they may occur any time during infusion[1,4,8] and rarely even shortly after the end of infusion.[2,3,5] Hence, the physician coverage would be for the entire duration of oxaliplatin infusion.

Some of the new drugs that have been added include ***alemtuzumab***, ***cetuximab***, ***oxaliplatin***, and ***tositumomab***.

References:

1. Bonosky K, Miller R. Hypersensitivity reactions to oxaliplatin: what nurses need to know. Clin J Oncol Nurs 2005;9(3):325-30.
2. Meyer L, Zuberbier T, Worm M, et al. Hypersensitivity reactions to oxaliplatin: cross-reactivity to carboplatin and the introduction of a desensitization schedule. J Clin Oncol 2002;20(4):1146-7.
3. Brandi G, Pantaleo MA, Galli C, et al. Hypersensitivity reactions related to oxaliplatin (OHP). Br J Cancer 2003;89(3):477-81.
4. Lenz G, Hacker UT, Kern W, et al. Adverse reactions to oxaliplatin: a retrospective study of 25 patients treated in one institution. Anticancer Drugs 2003;14(9):731-3.
5. Thomas RR, Quinn MG, Schuler B, et al. Hypersensitivity and idiosyncratic reactions to oxaliplatin.[see comment]. Cancer 2003;97(9):2301-7.
6. Bhargava P, Gammon D, McCormick MJ. Hypersensitivity and idiosyncratic reactions to oxaliplatin.[comment]. Cancer 2004;100(1):211-2.
7. Maindrault-Goebel F, Andre T, Tournigand C, et al. Allergic-type reactions to oxaliplatin: Retrospective analysis of 42 patients. Eur J Cancer 2005;41(15):2262-7.
8. Gowda A, Goel R, Berdzik J, et al. Hypersensitivity Reactions to oxaliplatin: incidence and management. Oncology (Huntingt) 2004;18(13):1671-5; discussion 6.

NURSING UPDATE

Nursing Articles of the Month. *Both these articles are available on-line for staff who has access to BCCA electronic journals BCCA staff through the library links provided.*

Cawley, M; and Benson, L. (2005). Current trends in managing oral mucositis. Clinical Journal of Oncology Nursing 9(5), 584–592. http://www.ons.org/publications/journals/CJON/Volume9/Issue5/0905toc.asp

Staat, K., and Segatore, M. (2005). The phenomen of chemo brain. Clinical Journal of Oncology Nursing 9(6), 6713-721. http://www.ons.org/publications/journals/CJON/Volume9/Issue6/0906toc.asp

IV Chemotherapy Setups

When new protocols are introduced, you might have questions about how to set up lines for infusion. For nurses working in multiple care settings you might find that different approaches are used, each of which is possibly acceptable and safe but simply different.

We therefore encourage you to consider the principles related to drug administration when setting up a system and to ask some key questions that will help you determine your best approach.

Ask yourself:

- Is your IV system based on having a primary setup with the chemo running via a secondary medication line? (Acknowledged exceptions to this are docetaxel, paclitaxel and etoposide, which must run through non-PVC tubing (See September 2005 ST Update).
- Does the setup keep the chemotherapy from mixing with all other meds and ***other*** chemotherapy?
- Is the flush solution compatible with ***all*** the medications you are planning on giving?
- Is there enough solution in the primary bag for flushes?
- Does your setup allow for infusion of other support medications if needed?
- Does your setup make it easy for you to give emergency drugs if necessary?
- Does your setup minimize risk of leakage/spills (i.e. luer-locked, secure connections)?
- Are there any special requirements for tubings i.e. non-PVC, special filters)?
- Is it cost-effective? Avoid using extra extension sets and Y-connectors unless absolutely necessary.

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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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