BC Cancer Agency

Systemic Therapy Update

Volume 8, Number 3 *for health professionals who care for cancer patients* March 2005
Website access at http://www.bccancer.bc.ca/STUpdate/

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EDITOR'S CHOICE

BC CANCER AGENCY LAUNCHES PROVINCIAL PRE-PRINTED CHEMOTHERAPY ORDERS

Provincial pre-printed chemotherapy orders will be launched on the BC Cancer Agency website on **April 4, 2005**. A task force of many key dedicated individuals at the BC Cancer Agency have been working diligently to create provincial pre-printed chemotherapy orders for each BC Cancer Agency chemotherapy treatment protocol. These standardized orders provide health care practitioners with have all the essential elements for a comprehensive chemotherapy order. The chemotherapy order mirrors the BC Cancer Agency chemotherapy treatment protocol and provides parameters for prescribing the treatments, preparing the treatments and administering the treatments.

The new provincial pre-printed chemotherapy orders will be found on the BC Cancer Agency website under Chemotherapy Protocols. Gradually, a hyperlink will be added to each protocol that will directly link to the corresponding pre-printed chemotherapy order.

The provincial pre-printed chemotherapy order should **always be used** in conjunction with the corresponding BC Cancer Agency chemotherapy treatment protocol and the relevant drug information. The Provincial Systemic Therapy Program (PSTP) recommends that all health care practitioners involved in chemotherapy delivery use the PSTP Policy entitled Chemotherapy Process as the guide to safe delivery of chemotherapy. This policy can be located on the BCCA website at: (www.bccancer.bc.ca/HPI/ChemotherapyProtocols/Policies)

Any health care professional using a BC Cancer Agency chemotherapy order to provide treatment for patients will be solely responsible for all aspects of the chemotherapy treatment including patient assessment, dose modifications, verifying drugs and the doses, providing the prescriptions and administering the medications according to acceptable standards of care.

If there are any questions or concerns, please contact the BC Cancer Agency, Provincial Drug Information Coordinator at (604) 877-6098, local 2247.

FOCUS ON SHORTENTED RITUXIMAB INFUSION TIMES

Administration of rituximab can be associated with substantial infusion-related toxicity, including hypersensitivity reactions causing fever, rash, cardiovascular and respiratory compromise and rarely a fatal cytokine release syndrome. Recent data suggest that a rapid (90-minute) rituximab infusion schedule in combination with a steroid containing chemotherapy regimen is well tolerated and safe when administered from the second infusion onward.

In early 2003, evidence became available suggesting that a shorter rituximab infusion time for the second and subsequent treatment cycles could be well tolerated (Blood 2003; 101:6-14). In March, 2004, a pilot study was undertaken at BCCA to investigate the safety of shortened rituximab infusion times (90 minutes) in patients with non-Hodgkin's lymphoma receiving second and subsequent cycles of rituximab in combination with CHOP (LYCHOP-R). In July, 2004, the Lymphoma Tumour Group revised the LYCHOP-R protocol to utilize the shorter rituximab infusion time for the second and subsequent treatment cycles. In September, 2004, LYCVPR (then called ULYCVPR) was introduced, also utilizing the same shorter infusion regimen for the second and subsequent rituximab infusions. Rituximab infusion time in cycle 1 of LYCHOP-R and LYCVPR remains at approximately 3 hours (longer if there is a hypersensitivity reaction necessitating infusion interruptions and re-starts at a lower rate). The shortened infusion time in subsequent cycles allows same day treatment of rituximab and CHOP or CVP, thereby enhancing treatment scheduling and resource utilization.

The results of the first 67 patients (163 treatments) in the pilot study were reported in a poster by Dr. Laurie Sehn at the December, 2004 meetings of the American Society of Hematology (ASH). The poster may be viewed at ASH website after signing on for free access (Poster Session 561-I, abstract 1407: "*Rapid infusion rituximab in combination with steroid containing chemotherapy can be given safely and substantially reduces resource utilization*".

Frequently-asked questions regarding the shortened rituximab infusion times:

Q: Can the shortened infusion time be utilized when rituximab is used as a single agent (e.g. LYRITUX)?
A: No. There are no data available at this time for the use of a shortened infusion time when rituximab is used as a single agent. LYRITUX is still given over at least 3 hours. (Clinical experience shows that the actual infusion time is more likely to be 4-5 hours). The current study is looking at shortened infusion time with LYCHOP-R and LYCVPR protocols only. These protocols include the use of prednisone which provides greater protection from untoward reactions to rituximab.

Q: If the patient has a hypersensitivity reaction on the first rituximab infusion administered using the standard infusion regimen, can subsequent infusions be administered over 90 minutes?
A: There are no established guidelines for this situation. We know that the risk of reaction is significantly less with the second infusion, so if the patient experienced only the usual minor reactions with the first infusion, we would proceed with the shortened infusion in the second cycle. However, if the patient had a major reaction with the first infusion, caution is necessary during the second infusion. The abstract states that the four patients who had adverse reactions to the initial infusion administered at the standard rate tolerated the shortened second infusion.

Q: The LYCHOP-R and LYCVPR protocols state that rituximab may be given on the same day as CHOP or CVP (day 1) or the following day (day 2), but no later than 72 hours after CHOP or CVP. What factors should be considered when deciding which day to give the rituximab?
A: Because the initial infusion of rituximab takes approximately 3 hours in addition to the time taken to give the CHOP portion of the regimen, the decision as to whether to give the CHOP and the rituximab on the same day might be driven by scheduling and resources available in the clinical area. Patients receiving all drugs on the same day must be brought in early enough to allow the treatment to be completed within the time available and also to ensure that physician coverage is available during the time of the rituximab infusion.

Q: Is there a minimum allowable period between the prednisone dose and the rituximab infusion?

A: There is no recommendation for a minimum time interval between the prednisone and the rituximab. Prednisone is given once daily in the morning on days 1 to 5 in the LYCHOP-R and LYCVPR protocols. Rituximab is administered at any time during the day, on day 1, 2 or 3. The protocol does state that prednisone must be taken prior to rituximab being administered, so if the patient arrives in the treatment area having forgotten to take the prednisone, he/she must take it then.

Q: The LYCHOP-R and LYCVPR protocols offer a choice of diluting rituximab in either 250 mL or 500 mL NS. Which volume is preferred?
A: Rituximab may be diluted to either 250 mL or 500 mL, provided that the final concentration is between 1 and 4 mg/mL. The choice of final volume may be determined by local preferences, although patient fluid status on rituximab treatment day should be considered. For example, if rituximab is administered on day 1, the fluids required to administer the CHOP or CVP given on day 1 may dictate the lower dilution volume for rituximab.

Q: Are data still being collected to further evaluate the shortened rituximab infusion times? If so, for how many more patients will data be collected and are centres outside the four BCCA Centres contributing data?
A: Data will continue to be collected until they are available from a total of 150-200 patients, at which time the results will be published. For consistency and ease of collection, data is being collected only from the four BC Cancer Agency Centres.

Reference

Byrd JC, Peterson BL, et al. Randomized phase 2 study of fludarabine with concurrent versus sequential treatment with rituximab in symptomatic, untreated patients with B-cell chronic lymphocytic leukemia: results from Cancer and Leukemia Group B 9712. Blood 2003; 101:6-14.

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DRUG UPDATE

Letrozole Therapy After Tamoxifen In October 2004, the BC Cancer Agency implemented the adjuvant letrozole therapy in postmenopausal women after five years of tamoxifen for early breast cancer (BRAJLET). To ensure that eligible women can consider this option after completion of tamoxifen therapy, letters have been sent out by the BC Cancer Agency Breast Tumour Group to the community oncologists and family physicians. In addition, a letter has been developed to provide information to patients who will complete or have recently completed their tamoxifen therapy.

The BC Cancer Agency Breast Cancer Outcomes Unit has determined the risk of recurrence after 5 years for various subgroups (see table). Nodal status (N0, 1-3 N+, 4-9 N+) was the strongest predictor of mortality in the second 5 years after diagnosis in patients completing adjuvant tamoxifen therapy. At 6-10 yrs, **Mortality** risks approximately **5%, 10%, and 20%** and **Event** risks approximately **10%, 15%, and 30%** were observed in patients with pathologic N0, 1-3 N+ and 4-9 N+ disease respectively.

After 5 years of tamoxifen, letrozole may:
- reduce the above risks by 40%
- be associated with a 1% risk of osteoporotic fracture if given for 3 years and approximately 2% if given for 5 years.

Women with low grade **T1N0** breast cancer should NOT routinely receive letrozole since the overall benefit is small.

Women with **node-positive** breast cancer have a ≥10% risk of mortality in the 5 years after a course of tamoxifen and SHOULD be offered letrozole.

In women with **T2N0** breast cancer, letrozole is reasonable therapy. The benefits and risks of Letrozole need to be carefully weighed considering the individual's risk of osteoporosis, her preferences to avoid further treatment and her concern about breast cancer recurrence.

RISK OF BREAST CANCER MORTALITY OR EVENT (A LOCAL, REGIONAL OR DISTANT RECURRENCE OR 2ND PRIMARY BREAST CANCER) AT 6-10 YEARS AFTER DIAGNOSIS IF DISEASE-FREE AFTER 5 YEARS OF TAMOXIFEN

PATHOLOGIC TMN STAGE	N	% BREAST CANCER MORTALITY AT 6-10 YRS	% BREAST CANCER 'EVENT' AT 6-10 YRS
N0	418	4	10
1-3 N+	380	9	15
4-9 N+	109	22	30
T1 (≤ 2cm)	561	5	12
T2 (2.1-5cm)	392	12	19
T1N0	252	2	10
T2N0	154	7	11

Details on the evidence to support this change are available on the BC Cancer Agency Cancer Management Guidelines of Breast Cancer (www.bccancer.bc.ca/HPI/CancerManagementGuidelines/Breast/Management/04DelayedAdjuvantTherapywithletrozole). Copies of the letters are available on our website with this March issue of the Update (www.bccancer.bc.ca/HPI/ChemotherapyProtocols/STUpdate).

CANCER MANAGEMENT GUIDELINES

The **Genitourinary (GU) Tumour Group** has developed two new management guidelines for prostate cancer:

- Brachytherapy (www.bccancer.bc.ca/HPI/CancerManagementGuidelines/Genitourinary/Prostate/Brachytherapy): the GU group has developed revised guidelines on the use of brachytherapy (interstitial radiotherapy) for the treatment of prostate cancer. Brachytherapy involves the use of placed radioactive implants (seed placement) into the prostate gland. The new guidelines provided patient eligibility for brachytherapy and certain special considerations:
  1. patients who are on anticoagulants
  2. patients who have had minimal transurethral prostatic resection (TUPR) may still be eligible
  3. The use of neoadjuvant/adjuvant androgen suppression for cytoreduction and in intermediate risk disease have been relaxed. Androgen deprivation therapy is still required in subgroups of patients with adverse risk factors but the use is discretionary in borderline cases.
- High-intensity focused ultrasound (HIFU) (www.bccancer.bc.ca/HPI/CancerManagementGuidelines/Genitourinary/Prostate/HIFU): the GU Group has carried out an evidence-based review on the efficacy data of HIFU in response to a number of queries regarding its effectiveness for the treatment of prostate cancer. HIFU is a technique using focused ultrasound to generate areas of intense heat and thus destroy tissue. It is increasingly being promoted as a non-invasive therapy for localized prostate cancer. However no randomized data exist to support its use and duration of follow-up from case series is short. The GU Tumour Group found that efficacy data does not allow meaningful assessment as to the benefit-risk ratio of HIFU treatment. Hence, HIFU cannot currently be recommended as a standard therapy but could be further explored in phase I-II studies monitored by ethical review board.

The **Breast Tumour Group** has incorporated the provincial guidelines developed by the BC Surgical Oncology Network for lymphatic mapping and sentinel node biopsy for breast cancer in the management guidelines (www.bccancer.bc.ca/HPI/CancerManagementGuidelines/Breast/Management/SentinelNodeBiopsy).

NURSING UPDATE

Evidence Impacting Practice:

Outcomes of Changes to Central Venous Catheters Flushing Procedures

In May 2004, changes were made to the Central Venous Catheters (CVC) Nursing Practice Directive and Procedures with an emphasis on changes in flushing procedures and routines. Ideally, these changes would reduce the time spent performing unnecessary interventions and reduce the number of invasive procedures performed on CVCs while preserving catheter patency. These changes reflected recommendations drawn from an extensive review of research and from the Canadian Intravenous Nursing Association and the Intravenous Nurses Society. The significant changes included:

- Increasing the flushing solution from 10 mL NS to 20 mL.
- Decreasing the concentration of the Heparin flush from Heparin 100 units/mL to 10 units/mL, and increasing the flush volume from 3 to 5 mL.
- Decreasing the frequency of flushing from every 24 hours to every 7 days. (The monthly flushing routine for ports remains unchanged).

The impact of these changes in practice was evaluated in all regional cancer centers over a 6-week period in November/December 2004. During that time, 885 CVCs were assessed. In 36 (4%) of those lines, nurses reported initial difficulties getting blood return or flushing. Of those 36 lines, 27 (75%) problems were resolved by conservative measures such as repositioning the patient. The other 9 (25%) problems needed to be resolved using alteplase. All 9 of these CVC's were effectively cleared using alteplase.

We conclude from this review that our complete occlusion rate for CVCs using the newly revised Directives and Procedures is 0%. We are pleased to report that we have therefore adopted the revised Directives and Procedures as standard practice, without further changes (www.bccancer.bc.ca/HPI/Nursing/References/NursingBCCA/default.htm)

We thank all the nurses who complied with the changes and who diligently recorded their assessments and interventions during the evaluation period.

Submitted by:
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HIGHLIGHTS OF PROTOCOL REVISIONS

Several protocols have been revised. The **Breast Tumour Group** has deleted the upper limit of 60 years based on chronological age for the **ACT regimen** (**doxorubicin, cyclophosphamide, paclitaxel**) (BRAJACT, BRAJACTG). The requirement for undesignated approval has also been removed from several protocols:

- **Gynecological Tumour Group:** Second-line treatment of advanced **ovarian cancer** using **carboplatin** and **gemcitabine** (GOOVCAG) and palliative re-treatment of **ovarian, tubal,** and **peritoneal cancer** using **vinorelbine** (GOOVVIN) revised.
- **Sarcoma Tumour Group:** Treatment of advanced c-kit positive gastrointestinal stromal cell tumours (GIST's) using imatinib (SAAVGI).

COMMUNITIES ONCOLOGY NETWORK

Online System for Cancer Drug Adjudication and Reimbursement (OSCAR) On 8 February, 2005, an e-mail package was sent out to all Communities Oncology Network (CON) hospitals who submit billings to BC Cancer Agency. The package included a survey and a tentative rollout plan. If you are a CON billing centre

but did not get the e-mail package, please contact Jeff Barnett, at jeff.bartnett@bccancer.bc.ca or at (250) 519-5519.

PATIENT EDUCATION

Patient Handout on Breast Cancer Treatment Protocol A new patient information handout has been developed for the adjuvant chemotherapy using cyclophosphamide, epirubicin and fluorouracil (BRAJFEC, sometimes also known as FEC 100).

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.

LIST OF NEW AND REVISED PROTOCOLS

The **INDEX to BC Cancer Agency Protocol Summaries** is revised monthly (includes 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 (age limit deleted): Adjuvant therapy for breast cancer using doxorubicin and cyclophosphamide followed by paclitaxel
- **BRAJACTG** revised (age limit deleted): Adjuvant Therapy for breast cancer using dose dense therapy: doxorubicin and cyclophosphamide followed by paclitaxel
- **BRAJCEFG** revised (cotrimoxazole deleted): Adjuvant therapy for breast cancer using cyclophosphamide, epirubicin, fluorouracil and filgrastim (G-CSF)
- **GOOVCAG** revised (undesignated approval replaced by class II): Treatment of advanced ovarian cancer in patients who have progressed or recurred following first-line platinum-based treatment using carboplatin and gemcitabine
- **GOOVVIN** revised (need for undesignated approval deleted): Palliative chemotherapy for re-treatment of ovarian, tubal, and peritoneal cancer using vinorelbine
- **GUBEP** revised (platelet added to Tests): Therapy for intermediate risk non-seminomatous testicular cancer using bleomycin, etoposide and cisplatin
- **GUEP** revised (platelet added to Tests): Therapy for nonseminoma germ cell cancer using Etoposide-Cisplatin
- **GUFUP** revised (platelet added to Tests): Combined modality therapy for squamous cell cancer of the genitourinary system using fluorouracil and cisplatin
- **GUPM** revised (platelet added to Tests): Therapy for hormone-resistant metastatic carcinoma of the prostate using mitomycin monotherapy
- **GUSCARB** revised (platelet added to Tests): Adjuvant therapy for stage I high risk seminoma using carboplatin
- **GUVIP2** revised (platelet added to Tests): Nonseminoma consolidation/salvage protocol using etoposide, cisplatin, ifosfamide, mesna
- **LUDOC** revised (eligibility clarified): Second-line treatment for advanced non-small cell lung cancer (NSCLC) with docetaxel (Taxotere®)
- **LYTHALID** revised (protocol code changed to MYTHALID): Therapy of multiple myeloma using thalidomide
- **MYTHALID** revised (protocol code changed from LYTHALID): Therapy of multiple myeloma using thalidomide
- **SAAVGI** revised (undesignated approval replaced by class II): Treatment of Advanced c-kit positive gastrointestinal stromal cell tumours (GIST's) using imatinib (Gleevec®)

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, Chemotherapy 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.

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.

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Most items have been hyperlinked for easy access

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