BC Cancer Agency

Systemic Therapy Update

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INSIDE THIS ISSUE

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

EDITOR'S CHOICE

HIGHLIGHTS OF PROTOCOLS AND PRE-PRINTED ORDERS

Beginning **October 1, 2005**, all etoposide intravenous infusions at the BC Cancer Agency are to be prepared in non-polyvinyl chloride (PVC) bags and administered through non-PVC tubings. This change is to minimize additional patient exposure to diethylhexyl phthalate (DEHP), which is potentially hepatotoxic and carcinogenic. All etoposide-based treatment protocols and pre-printed doctor's orders have been revised. This affects a number of protocols for several tumour sites (brain, genitourinary, gynecological, head and neck, lung, lymphoma, sarcoma). The complete list can be found under the List of New and Revised Protocols.

For more background on this change, see the September issue of the Systemic Therapy Update (vol. 8, no.9).

FOCUS ON SINGLE AGENT PEMETREXED IN NON-SMALL CELL LUNG CANCER

Non-small cell lung cancer (NSCLC) treatment varies according to tumour stage at time of diagnosis. In advanced NSCLC, platinum-based doublets are the standard of care in the first-line setting.[1-3] Traditionally, docetaxel is the main second-line therapy based on its survival advantage over best supportive care.[1,2] Recently, the FDA in the United States has also approved pemetrexed as an alternative second-line therapy for advanced NSCLC. This is based on a study showing similar survival to docetaxel while having less hematologic toxicity.

The use of pemetrexed for NSCLC is under review by the BC Cancer Agency. At present, pemetrexed is a benefit drug only when used with platinum in the treatment of malignant mesothelioma.[10] This article will review the current literature on pemetrexed, a novel multitargeted antifolate, and its role in NSCLC.

Purine and pyrimidines are the basic building blocks of DNA and have been targeted for cancer therapy for several decades.[4] Pemetrexed inhibits tumour growth by inhibiting three main metabolic enzymes in the purine and pyrimidine biosynthetic pathways; two folate dependent enzymes, thymidylate synthase (TS) and dihyrofolate reductase (DHFR), and the purine biosynthesis enzyme, glycinamide ribonucleotide formyl

transferase (GARFT). A third folate dependent enzyme inhibited by pemetrexed has also been identified; aminoimidazole carboxamide ribonucleotide formyl transferase (AICARFT).[5]

One of the primary targets of pemetrexed action is inhibition of TS, which results in decreased thymidine necessary for DNA synthesis. However, inhibition of the other folate enzymes are important for pemetrexed's clinical activity, as demonstrated by its activity against H630 colon cancer cell lines, which are resistant to raltitrexed and 5-fluorouracil due to TS amplification.[4]

As a single agent, pemetrexed has been studied in both the first- and second-line settings. In previously untreated, surgically incurable NSCLC patients, Clark et al.[6] studied pemetrexed 600 mg/m^2 q3weeks (10 min IV infusion) in 59 patients in Australia and South Africa in a phase II trial. In 57 evaluable patients, the overall response rate was 16% (9 partial remissions), with a median time to progression of 4.4 months, and a median duration of response of 4.9 months. The median survival was 7.2 months, and the one-year survival rate was 32%.

Rusthoven et al.[7] studied pemetrexed 600 mg/m^2 q3 weeks (10 min IV infusion) in 33 patients with previously untreated, unresectable advanced NSCLC in a phase II trial. The dose was reduced to 500 mg/m^2 after severe toxicity was seen in the first three patients (grade 3/4 neutropenia, febrile neutropenia, grade 4 thrombocytopenia, skin rash). In 30 evaluable patients, a partial response was achieved in 23%, with a median time to progression of 3.8 months, and a median duration of response of 3.1 months. The median survival was 9.2 months, and one-year survival rate was 25%.

Smit et al.[8] studied the use of pemetrexed in second-line treatment of NSCLC. This was a phase II trial with 81 patients. Pemetrexed was dosed at 500 mg/m^2 q3weeks (10 min. IV infusion). Dexamethasone was given to prevent skin rash at a dose of 4mg PO bid for 3 days, starting one day prior to treatment. Of 79 evaluable patients, 44 patients had progressed after prior platinum-containing treatment, and 35 had progressed on non-platinum regimens. The overall response rate was 8.9 % (6 partial responses, 1 complete response), the median time to progressions was 2 months, and the median duration of response was 6.8 months. The median survival time was 5.7 months.

As a result of the Smit trial, Hanna et al.[9] studied 571 patients in a phase III trial comparing pemetrexed to docetaxel in advanced NSCLC previously treated with chemotherapy. Docetaxel 75 mg/m^2 q3 weeks (1 hour IV infusion) was given to 288 patients, and 283 patients received pemetrexed 500 mg/m^2 q3 weeks (10 min IV infusion). Both arms received prophylactic dexamethasone. To reduce both hematologic and non-hematologic toxicities, patients on the pemetrexed arm received folic acid 350-1000 mcg daily, starting 1-2 weeks prior to treatment and continuing until 3 weeks after completion, and vitamin B12 1000 mcg q9weeks, starting 1 week prior to first treatment. In summary, pemetrexed and docetaxel have similar efficacy with respect to response rate (9.1% vs. 8.8%), median survival (8.3 vs. 7.9 months) and progression-free survival (2.9 months each). The one-year survival rate was 29.7% in each arm. However, pemetrexed had a favourable hematologic toxicity profile as compared to docetaxel. Grade 3 or 4 neutropenia was 5.3% for pemetrexed vs. 40.1% for docetaxel, febrile neutropenia was 1.9% vs. 12.7%, hospitalizations due to febrile neutropenia were 1.5% vs. 13.4%, and GCSF support was required in 2.6% vs. 19.2%. These differences were all statistically significant with a p value of < 0.001. The FDA in the United States approved pemetrexed as second-line therapy for advanced NSCLC on the basis of this trial.

Pemetrexed is also being studied for NSCLC in combination with cisplatin, carboplatin, gemcitabine, and vinorelbine.[3]

In summary then, pemetrexed as a single agent demonstrates promising activity in advanced NSCLC. With the addition of dexamethasone, Vitamin B12 and folic acid, the toxicity profile has improved significantly, and pemetrexed is a possible alternative to docetaxel in the second-line setting. Further research is needed to define the role of pemetrexed in first-line treatment of advanced NSCLC.

References

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CANCER DRUG MANUAL

Several drug monographs and patient information handouts have been revised.

Cytarabine Monograph

A typo is corrected in the paragraph on risks for cerebellar toxicity where it should read "….patients older than 60 years of age…" rather than "….patients < 60 years of age…".

Etoposide Monograph

The major revision involves the clarification of the preparation of an oral solution from the etoposide injectable.

Fluorouracil Monograph and Handout

These have been revised to include information about a drug interaction between fluorouracil and warfarin. There have been several case reports of increased international normalized ratio (INR) and bleeding when warfarin and fluorouracil are used concurrently. More recently, in a retrospective study of patients treated with fluorouracil and "minidose" warfarin (1 mg daily for prophylaxis of central venous catheter-related thrombosis), 33% of patients had INR elevation and 8% experienced bleeding. The revised monograph recommends adjustment of warfarin as dosed based on the following monitoring parameters:

1. a baseline INR for all patients starting concurrent fluorouracil and warfarin, and
2. weekly INR during therapy and one month after.

The revised handout also includes caution on this potential interaction.

Oxaliplatin Monograph and Handout

These have been revised to include information about calcium and magnesium prophylaxis for peripheral neuropathy, as well as a possible drug interaction between oxaliplatin and warfarin. In the study mentioned above, under fluorouracil, patients on the fluorouracil/oxaliplatin combination (FOLFOX) regimen were twice as likely to have INR abnormalities as patients on other regimens. This potential interaction between oxaliplatin and warfarin, or potentiation of the fluorouracil-warfarin interaction by oxaliplatin, has not been definitively established. Nevertheless, the revised monograph recommends the same monitoring parameters for oxaliplatin as for fluorouracil. The revised handout also includes this potential interaction.

BENEFIT DRUG LIST

The following changes to the Benefit Drug List are **effective 1 October 2005**:

Drug	*Indication*	*Benefit status*
Gemcitabine	treatment of metastatic breast cancer using gemcitabine and paclitaxel (BRAVGEMT)	added as Class II
Paclitaxel	treatment of metastatic breast cancer using gemcitabine and paclitaxel (BRAVGEMT)	added as Class I

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:

- **BRAVGEMT** new: Treatment of metastatic breast cancer using gemcitabine and paclitaxel

Revised protocols:

- **CNCARV** revised (use of non-PVC equipment added): Therapy for recurrent ependymoma using carboplatin and etoposide
- **CNIME** revised (use of non-PVC equipment added): Ifosfamide, mesna and etoposide in the treatment of recurrent brain tumours
- **GOBEP** revised (use of non-PVC equipment added): Therapy of non-dysgerminomatous ovarian germ cell cancer using bleomycin, etoposide and cisplatin
- **GOCXADV** deleted: Treatment of advanced/recurrent non-small cell cancer of the cervix with carboplatin and docetaxel in ambulatory care settings
- **GOEP** revised (use of non-PVC equipment added): Therapy of dysgerminomatous ovarian germ cell cancer using cisplatin and etoposide
- **GOOVETO** revised (use of non-PVC equipment added): Therapy for relapsed/progressive "ovarian" cancer using etoposide
- **GOSMCC2** revised (use of non-PVC equipment added): Treatment of small cell carcinoma of cervix using paclitaxel, cisplatin, etoposide and carboplatin with radiation
- **GUBEP** revised (use of non-PVC equipment added): Therapy for intermediate risk non-seminomatous testicular cancer using bleomycin, etoposide and cisplatin
- **GUEP** revised (use of non-PVC equipment added): Therapy for nonseminoma germ cell cancer using etoposide-cisplatin
- **GUPDOC** revised (PSA test added): Palliative therapy for metastatic hormone refractory prostate cancer using docetaxel
- **GUSCPE** revised (use of non-PVC equipment added): Therapy of genitourinary small cell tumors with a platin and etoposide
- **GUVIP2** revised (use of non-PVC equipment added): Nonseminoma consolidation/salvage protocol using etoposide, cisplatin, ifosfamide, mesna
- **HNDE** revised (use of non-PVC equipment added): Therapy for recurrent and metastatic nasopharyngeal cancer using cisplatin and etoposide
- **HNPE** revised (use of non-PVC equipment added): Intensive cisplatin and etoposide chemotherapy for recurrent and metastatic head and neck cancer
- **LUAJEP** revised (use of non-PVC equipment added): Adjuvant cisplatin and etoposide following resection of stage I, II and IIIA non-small cell lung cancer
- **LUAJNP** revised (reference updated): Adjuvant cisplatin and vinorelbine following resection of stage I, II and IIIA non-small cell lung cancer

- **LUALTL** revised (use of non-PVC equipment added): Therapy for limited stage SCLC using alternating CAV/EP plus early thoracic irradiation using cyclophosphamide, doxorubicin, vincristine, etoposide and cisplatin
- **LUAVPG** revised (administration sequence clarified): Treatment of advanced non-small cell lung cancer (NSCLC) with platinum and gemcitabine
- **LUMMPG** revised (administration sequence clarified): Treatment of malignant mesothelioma with platinum and gemcitabine
- **LUMMPPEM** revised (administration sequence clarified): Treatment of malignant mesothelioma with platinum and pemetrexed (Alimta®)
- **LUPAVESE** revised (use of non-PVC equipment added): Treatment for extensive stage small cell lung cancer (SCLC) with cisplatin, doxorubicin, vincristine and etoposide (PAVE)
- **LUPAVESL** revised (use of non-PVC equipment added): Treatment for limited stage small cell lung cancer (SCLC) with cisplatin, doxorubicin, vincristine and etoposide (PAVE), and cisplatin and etoposide (EP) concurrent with early thoracic irradiation
- **LUPE** revised (use of non-PVC equipment added): Palliative Therapy of selected solid tumours using cisplatin and etoposide (interim version)
- **LUPESL** revised (use of non-PVC equipment added): Treatment for limited stage small cell lung cancer (SCLC) with etoposide and cisplatin (EP) and early thoracic irradiation
- **LYECV** revised (use of non-PVC equipment added): Consolidation for lymphoma using etoposide and cyclophosphamide
- **LYODBEP** deleted: Treatment of Hodgkin's disease in elderly patients with vincristine, doxorubicin, bleomycin, etoposide and prednisone
- **LYPALL** revised (use of non-PVC equipment added): Lymphoma palliative chemotherapy
- **SAIME** revised (use of non-PVC equipment added): Etoposide, ifosfamide-mesna for patients with newly diagnosed Ewing's sarcoma/peripheral neuroectodermal tumor (PNET) or rhabdomyosarcoma or advanced soft tissue or bony sarcomas

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.

New pre-printed order:

- **BRAVGEMT** new: Treatment of metastatic breast cancer using gemcitabine and paclitaxel

Revised pre-printed orders:

- **CNCARV** revised (use of non-PVC equipment added): Therapy for recurrent ependymoma using carboplatin and etoposide
- **CNIME** revised (use of non-PVC equipment added): Ifosfamide, mesna and etoposide in the treatment of recurrent brain tumours
- **GOBEP** revised (use of non-PVC equipment added): Therapy of non-dysgerminomatous ovarian germ cell cancer using bleomycin, etoposide and cisplatin
- **GOCXADV** deleted: Treatment of advanced/recurrent non-small cell cancer of the cervix with carboplatin and docetaxel in ambulatory care settings
- **GOEP** revised (use of non-PVC equipment added): Therapy of dysgerminomatous ovarian germ cell cancer using cisplatin and etoposide
- **GOOVETO** revised (use of non-PVC equipment added): Therapy for relapsed/progressive "ovarian" cancer using etoposide
- **GOSMCC2** revised (use of non-PVC equipment added): Treatment of small cell carcinoma of cervix using paclitaxel, cisplatin, etoposide and carboplatin with radiation
- **GUBEP** revised (use of non-PVC equipment added): Therapy for intermediate risk non-seminomatous testicular cancer using bleomycin, etoposide and cisplatin
- **GUEP** revised (use of non-PVC equipment added): Therapy for nonseminoma germ cell cancer using etoposide-cisplatin

- **GUPDOC** revised (PSA test added): Palliative therapy for metastatic hormone refractory prostate cancer using docetaxel
- **GUSCPE** revised (use of non-PVC equipment added): Therapy of genitourinary small cell tumors with a platin and etoposide
- **GUVIP2** revised (use of non-PVC equipment added): Nonseminoma consolidation/salvage protocol using etoposide, cisplatin, ifosfamide, mesna
- **HNDE** revised (use of non-PVC equipment added): Therapy for recurrent and metastatic nasopharyngeal cancer using cisplatin and etoposide
- **HNPE** revised (use of non-PVC equipment added): Intensive cisplatin and etoposide chemotherapy for recurrent and metastatic head and neck cancer
- **LUAJEP** revised (use of non-PVC equipment added): Adjuvant cisplatin and etoposide following resection of stage I, II and IIIA non-small cell lung cancer
- **LUAJNP** revised (reference updated): Adjuvant cisplatin and vinorelbine following resection of stage I, II and IIIA non-small cell lung cancer
- **LUALTL** revised (use of non-PVC equipment added): Therapy for limited stage SCLC using alternating CAV/EP plus early thoracic irradiation using cyclophosphamide, doxorubicin, vincristine, etoposide and cisplatin
- **LUAVPG** revised (administration sequence clarified): Treatment of advanced non-small cell lung cancer (NSCLC) with platinum and gemcitabine
- **LUMMPG** revised (administration sequence clarified): Treatment of malignant mesothelioma with platinum and gemcitabine
- **LUMMPPEM** revised (administration sequence clarified): Treatment of malignant mesothelioma with platinum and pemetrexed (Alimta®)
- **LUPAVESE** revised (use of non-PVC equipment added): Treatment for extensive stage small cell lung cancer (SCLC) with cisplatin, doxorubicin, vincristine and etoposide (PAVE)
- **LUPAVESL** revised (use of non-PVC equipment added): Treatment for limited stage small cell lung cancer (SCLC) with cisplatin, doxorubicin, vincristine and etoposide (PAVE), and cisplatin and etoposide (EP) concurrent with early thoracic irradiation
- **LUPDOC** revised (dilution volume clarified): Second-line treatment of advanced non-small cell lung cancer (NSCLC) with docetaxel (Taxotere®)
- **LUPE** revised (use of non-PVC equipment added): Palliative Therapy of selected solid tumours using cisplatin and etoposide (interim version)
- **LUPESL** revised (use of non-PVC equipment added): Treatment for limited stage small cell lung cancer (SCLC) with etoposide and cisplatin (EP) and early thoracic irradiation
- **LYECV** revised (use of non-PVC equipment added): Consolidation for lymphoma using etoposide and cyclophosphamide
- **LYODBEP** deleted: Treatment of Hodgkin's disease in elderly patients with vincristine, doxorubicin, bleomycin, etoposide and prednisone
- **MOIT** revised (lab appointments clarified): Therapy for solid tumours using intrathecal methotrexate and/or thiotepa and/or cytarabine
- **SAIME** revised (use of non-PVC equipment added): Etoposide, ifosfamide-mesna for patients with newly diagnosed Ewing's sarcoma/peripheral neuroectodermal tumor (PNET), rhabdomyosarcoma or advanced soft tissue or bony sarcomas

CONTINUING EDUCATION – MARK YOUR CALENDAR

- **2-5 October 2005**: Annual Canadian Association of Nurses in Oncology Conference, Moncton, New Brunswick (www.cos.ca/cano) – registration now open
- **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/) – registration and poster submission now open
- **3-5 November 2005**: BCCA Annual Cancer Conference, Westin Bayshore 1601 Bayshore Drive, Vancouver, BC (www.bccancer.bc.ca/HPI/AnnualConference/default.htm) – registration and poster submission now open

WEBSITE RESOURCES

The followings 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

IN TOUCH	www.bccancer.bc.ca	bulletin@bccancer.bc.ca
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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	jbarnett@bcancer.bc.ca
Drug Information	Ext 6275	druginfo@bccancer.bc.ca
Library / Cancer Information	1-888-675-8001 Ext 8001	requests@bccancer.bc.ca
OSCAR Hotline	1-888-355-0355	
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Vancouver Island Centre (VICC)	(250) 519-5500	Toll-Free 1-(800) 670-3322