BC Cancer Agency
CARE & RESEARCH

Systemic Therapy Update

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INSIDE THIS ISSUE

EDITOR'S CHOICE

DASATINIB ADDED TO BC CANCER AGENCY BENEFIT DRUG

Dasatinib, an oral tyrosine kinase inhibitor, has been added to the Benefit Drug List for the management of patients with chronic myeloid leukemia (CML). The protocol ULKCMLD is for:

1. patients with chronic phase CML resistant to imatinib therapy
2. patients with accelerated/blast phase CML (including Ph+ acute lymphoblastic leukemia [ALL]) who are intolerant to imatinib.

Note that the dose regimen in the protocol differs from that recommended by the manufacturer (see Dosage in the following article). The BCCA Compassionate Access Program (CAP) approval is required prior to the initiation of treatment (please refer to https://cap.phsa.ca/). Patients will be provided with monthly supply of the drug by the regional and community cancer centres.

More information will be available in future issues of the Update regarding patients currently accessing dasatinib via the PATHWAYS to SPRYCEL™ Program of Bristol-Myers Squibb.

FOCUS ON DASATINIB

Dasatinib (SPRYCEL®, Bristol-Myers Squibb) has recently been granted conditional approval by Health Canada for the treatment of adults with chronic, accelerated, or blast phase chronic myeloid leukemia (CML) with resistance or intolerance to prior therapy, including imatinib. Dasatinib is an oral tyrosine kinase inhibitor, similar to imatinib, with demonstrated activity in resistant disease. Dasatinib is available as 20 mg, 50 mg, and 70 mg film-coated tablets. The list price per tablet is $34.22, $68.43 and $75.45, respectively.

Dosage

The BCCA protocol ULKCMLD recommends once daily dosing of 100 mg for chronic phase CML and 140 mg for accelerated phase CML, blast phase CML or Ph+ acute lymphoid leukemia (ALL). This differs from that the 70 mg twice daily dosing recommended by the manufacturer.[1] The ULKCMLD dosing is based on reports that similar efficacy can be achieved with lower toxicity.[2,3]

Pharmacology

CML is associated with over-activity of the ABL tyrosine kinase enzyme. Imatinib is a potent inhibitor of ABL kinase, but resistance or intolerance to its effects, resulting in disease relapse, remain problematic.[4] Dasatinib differs from imatinib in that it binds more effectively to tyrosine kinase even with mutations that would render the enzyme resistant to imatinib.[4] Dasatinib has also been shown to be more potent against the kinase, thereby optimizing response and delaying or preventing mutations and subsequent resistance.[5]

Adverse effects

Myelosuppression is common but usually reversible with dose reduction or delay.[4,6] Neutropenia, anemia, and thrombocytopenia are more common with advanced phase CML and Ph+ ALL.[1] Most non-hematologic toxicities are mild to moderate in severity (see table).[7,8]

Adverse effect	**70 mg BID**
Hematological	neutropenia (severe 49-83%),[9] thrombocytopenia (severe 48-83%),[9] anemia (severe 18-70%)[9]
Cardiovascular	heart failure/cardiac dysfunction 5% (severe 3%), pericardial effusion 4% (severe 1%)
Pulmonary	dyspnea 31% (severe 7%), pleural effusions 17% (severe 5%),[7] pulmonary infiltration 1-5%
Hemorrhage	41% (severe 11%), including gastrointestinal hemorrhage 13% (severe 8%)
Lymphatics	fluid retention 49% (severe 9%), peripheral edema[4,10] 14-19% (severe 0%)
Others	rash 34% (severe 1%),[11] diarrhea 48% (severe 5%), musculoskeletal pain 38% (severe 5%)

Adapted from standard reference[1] unless specified otherwise.

Preliminary data suggest that once daily dosing may be associated with more favorable toxicity profiles compared to the 70 mg twice daily dosing.[2,3]

Adverse Effect	***CHRONIC PHASE CML[2]***		***ADVANCED PHASE CML[3]***	
	70 mg BID	***100 mg once daily***	***70 mg BID***	***140 mg once daily***
Neutropenia	severe 41%	severe 33%	87% (severe 70%)	85 (severe 65%)
Thrombocytopenia	severe 37%	severe 22%	92% (severe 70%)	89 (severe 68%)
Pericardial effusion	16% (all grades)	7% (all grades)	4% (severe 1%)	<1% (severe 0%)
Pleural effusions	16% (all grades)		23% (severe 6%)	16% (severe 5%)
Peripheral edema			13% (severe 1%)	6% (severe <1%)

Drug and Food Interactions[1]

Dasatinib is rapidly and extensively metabolized by CYP3A4 enzymes. Therefore, grapefruit juice and drugs which inhibit CYP3A4 may decrease the metabolism of dasatinib, whereas drugs which induce CYP3A4 may have the opposite effect. Dasatinib is a CYP3A4 inhibitor, thus reducing the clearance of drugs that are primarily metabolized by CYP3A4 (e.g. simvastatin).

Caution is required for patients taking anti-arrhythmics, other medications that may lead to QT prolongation, or high cumulative doses of anthracyclines. Patients who are at increased risk of bleeding as a result of anticoagulants also require additional caution.

Antacids or drugs that suppress gastric acids may reduce the absorption of dasatinib, so caution is necessary if they are used concurrently with dasatinib. For short-term acid suppression, antacids are preferred and it is recommended that they be taken at least *2 hours before or after* the dasatinib dose.

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References

1. Bristol-Myers Squibb Canada. SPRYCEL® Product Monograph. Montreal, Quebec; 16 July 2007.
2. Shah NP, Kim DW, Kantarjian HM, et al. Dasatinib 50 mg or 70 mg BID compared to 100 mg or 140 mg QD in patients with CML in chronic phase (CP) who are resistant or intolerant to imatinib: One-year results of CA180034. J Clin Oncol (Meeting Abstracts) 2007;25(18_suppl):7004.
3. Pasquini R, Ottmann OG, Goh YT, et al. Dasatinib 140 mg QD compared to 70 mg BID in advanced-phase CML or Ph(+) ALL resistant or intolerant to imatinib: One-year results of CA180-035. J Clin Oncol (Meeting Abstracts) 2007;25(18_suppl):7025-.
4. Talpaz M, Shah NP, Kantarjian H, et al. Dasatinib in imatinib-resistant Philadelphia chromosome-positive leukemias. N Engl J Med 2006;354(24):2531-41.
5. Shah NP, Tran C, Lee FY, et al. Overriding imatinib resistance with a novel ABL kinase inhibitor. Science 2004;305(5682):399-401.
6. Hochhaus A, Kantarjian HM, Baccarani M, et al. Dasatinib induces notable hematologic and cytogenetic responses in chronic-phase chronic myeloid leukemia after failure of imatinib therapy. Blood 2007;109(6):2303-9.
7. Shah NP. Dasatinib. Drugs of Today 2007;43(1):5-12.
8. Lipton JH, Forrest DL, Gambacorti-Passerini C, et al. Recommendations for the Management of Imatinib-Resitant/Intolerant Chronic Myeloid Leukemia (CML) Patients with the Kinase Inhibitor, SPRYCEL® (Dasatinib). 2007. Available from www.canadianhematologysociety.org. Accessed 15 October 2007.
9. Rose BD, editor. Dasatinib. Waltham, Massachusetts: UpToDate 15.2; 2007.
10. Cortes JE, Kim DW, Rosti G, et al. Dasatinib (D) in patients (pts) with chronic myelogenous leukemia (CML) in myeloid blast crisis (MBC) who are imatinib-resistant (IM-R) or IM-intolerant (IM-I): Results of the CA180006 'START-B' study. J Clin Oncol (Meeting Abstracts) 2006;24(18_suppl):6529-.
11. The NCCN Chronic Myelogenous Leukemia Clinical Practice Guidelines in Oncology (Version 2.2008). © 2007 National Comprehensive Cancer Network, Inc. Available from http://www.nccn.org. Accessed 9 October 2007.

CANCER DRUG MANUAL

Bromocriptine and Cabergoline Monographs have been developed for both dopamine agonists, with corresponding patient handouts for bromocriptine (new) and cabergoline (updated). Expert review was provided by Dr. Michelle Johnson (Endocrinologist, St Paul's Hospital, Vancouver). Both drugs are currently funded for the treatment of pituitary tumours. The major side effects – nausea, lightheadedness after standing, somnolence – usually occur with treatment initiation or dose increase. These may be minimized by:

- starting with a low dose and increasing the dose slowly
- using small doses more frequently
- taking the drug with food or at bedtime

Highlighted cabergoline handout changes include:

- addition of statement on cross reactivity with other ergot derivatives
- recommendation to take with food to improve gastrointestinal symptoms

Dasatinib Interim Monograph and Patient Handout have been created. A complete, peer-reviewed version will be available next month.

Ifosfamide Monograph and Patient Handout have been completely revised. Expert review was provided by Dr. Meg Knowling (Sarcoma Tumour Group). Highlighted monograph changes include:

- more details added to the Dosage Guidelines

- extravasation risk has been reclassified from non-vesicant to irritant to be consistent with other standard references
- new guidelines added for dose reduction in patients with renal and hepatic dysfunction

Handout changes include:

- updated side effect and management statements

Mesna Monograph and Patient Handout have been completely revised. Expert review was provided by Dr. Meg Knowling (Sarcoma Tumour Group). Highlighted monograph changes include:

- expanded Interactions table
- modified Dosage Guidelines with details on various dosing regimens

Handout changes include:

- Injection and Oral handouts have been combined to facilitate counselling of patients receiving mesna by both routes
- addition of Side Effects and Management table

Chemotherapy Preparation and Stability Chart has been revised with the following:

- Routine review and updating: ifosfamide and mesna

EMERGENCY AID DRUG PROGRAM: DRUG BENEFIT LIST CHANGES

The Emergency Aid Drug Program (EADP) is a service provided to patients who need financial assistance for supportive care medications related to chemotherapy and radiation therapy. It is co-managed by the BC Cancer Agency (BCCA) and the Canadian Cancer Society (CCS). As it is a program with limited funding, the EADP should be considered a last option. Patients should initially be referred to Patient and Family Counselling to ensure other funding options have been exhausted. The CCS volunteers will conduct a private financial means evaluation for patients and will recommend the level of assistance required to the BCCA. Once approved, the benefits are active for a one-year term and generally restricted to drugs on the EADP benefit list, which is available on the BCCA website:

www.bccancer.bc.ca/RS/CommunitiesOncologyNetwork/Emergency+Aid+Drug+Program/default.htm

Note that coverage is for the Pharmacare Low Cost Alternative brand of all medications where applicable and all requirements for Pharmacare Special Authority must be met for any drug to be an EADP benefit.

The following additions and deletions to the EADP benefit list are effective immediately.

Additions

Drug	***Coverage****
Amoxicillin/clavulanate	Oral solid dosage forms (max.14-day supply)
Clarithromycin	Oral solid dosage forms (max.14-day supply)
Fluconazole	Oral solid dosage forms (max.10-day supply)
Levofloxacin	Oral solid dosage forms (max.7-day supply)
Metronidazole	Compounded oral liquid (max. 10-day supply and total cost $30.00)
Moxifloxacin	Oral solid dosage forms (max.10-day supply)
Norfloxacin	Oral solid dosage forms (max.10-day supply)
Ondansetron	Now also covers for patients registered with the Pharmacare Palliative Care Benefits Program as long as patients are receiving palliative chemotherapy or radiation therapy only

Ranitidine	Oral solid dosage forms (max. dose of 150 mg BID); not for pre-existing conditions
Valacyclovir	Oral solid dosage forms (max.10-day supply)

* for full details, go to: www.bccancer.bc.ca/RS/CommunitiesOncologyNetwork/Emergency+Aid+Drug+Program/default.htm

Deletions

- Anethole
- Trithione
- Gentamicin (all dosage forms)
- Neomycin
- Pilocarpine eye drops

PROVINCIAL SYSTEMIC THERAPY PROGRAM POLICIES

Prevention and Management of Extravasation of Chemotherapy (Policy III-20) The extravasation hazard of ifosfamide has been changed from non-vesicant to irritant to conform with standard references.

LIST OF NEW AND REVISED PROTOCOLS, PRE-PRINTED ORDERS AND PATIENT HANDOUTS

BC Cancer Agency Protocol Summaries, Provincial Pre-Printed Orders (PPPOs) and Patient Handouts are revised periodically. New and revised protocols, PPPOs and patient handouts for this month are listed below. Protocol codes for treatments requiring "Compassionate Access Program" approval are prefixed with the letter **U**.

NEW PROTOCOLS, PPPOS AND PATIENT HANDOUTS (AFFECTED DOCUMENTS ARE CHECKED):

CODE	Protocol	PPPO	Patient Handout	Protocol Title
UBRAVBR	☑	☑	☐	Palliative Therapy for Metastatic Breast Cancer using nanoparticle, albumin-bound (nab)-Paclitaxel (ABRAXANE®)
GIGECF	☑	☑	☑	Perioperative Treatment of Resectable Adenocarcinoma of the Stomach, Gastroesophageal Junction or Lower 1/3 Esophagus using Epirubicin, Cisplatin and Infusional Fluorouracil
ULKCMLD	☑	☑	☑	Treatment of Chronic Myeloid Leukemia (CML) Using Dasatinib (SPRYCEL®)

REVISED PROTOCOLS, PPPOS AND PATIENT HANDOUTS (AFFECTED DOCUMENTS ARE CHECKED):

CODE	Protocol	PPPO	Patient Handout	Changes	Protocol Title
CNAJTZRT	☑	☑	☐	*liver function tests and serum creatinine clarified in protocol, return appointment and lab work section clarified in PPPO*	Concomitant and Adjuvant Temozolomide for Newly Diagnosed Malignant Gliomas
CNCCNU	☑	☑	☐	*CBC and diff, platelets added to Day 28 under Test section*	Lomustine (CCNU) for Treatment of Recurrent Malignant Brain Tumours
GUBCV	☐	☑	☐	*clarification of required bloodwork*	Therapy for transitional cell cancers using Carboplatin-Vinblastine

CODE	Protocol	PPPO	Patient Handout	Changes	Protocol Title
GUBEP	☑	☑	☐	*dilution volume for etoposide clarified*	Treatment with Bleomycin, Etoposide, Cisplatin for Germ Cell Cancers
GUFUPRT	☐	☑	☐	*fluorouracil dosing clarified*	Therapy for Squamous Cell Cancer of the Genitourinary System Using Fluorouracil and Cisplatin with Radiation
LYCHOP	☑	☐	☐	*typo corrected for bilirubin unit*	Treatment of Lymphoma with Doxorubicin, Cyclophosphamide, Vincristine and Prednisone (CHOP)
LYCHOPR	☑	☐	☐	*typo corrected for bilirubin unit*	Treatment of Lymphoma with Doxorubicin, Cyclophosphamide, Vincristine, Prednisone and Rituximab (CHOP-R)

CONTINUING EDUCATION

BC Cancer Agency Annual Cancer Conference 2007 will be held on **29 November – 1 December**, at the Westin Bayshore Resort & Marina in Vancouver. This three-day conference is the BC Cancer Agency's premier professional development, learning and networking event. It is the only Western Canadian event of its kind, attracting 1000-plus professionals working in the oncology field.

This year's theme, *Innovation and Technology – Bench to Bedside,* creates the framework for our examination of the role of the BC Cancer Agency and its partners in the 'living laboratory' of British Columbia and their endeavours to enhance population-based cancer control outcomes. A highlight of this year's conference is a keynote presentation on November 30 by Dr. Roberta Bondar, a space scientist, neurologist, author, astronaut and Canada's first woman in space.

For a detailed agenda, schedule and registration information, please visit: www.bccancer.bc.ca/HPI/ACC2007/default

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, COMPASSIONATE ACCESS PROGRAM (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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