Practice Guideline: Systemic Therapy Summary

Treatment of Relapsed/Refractory Anaplastic Large Cell Lymphoma with Brentuximab Vedotin
(LYMP – Brentuximab vedotin)

Lymphoproliferative Disorders Disease Site Group

Effective: January 2014
Updated: April 2015
ACKNOWLEDGEMENT AND SPONSORSHIP DISCLAIMERS

There are no relevant conflicts of interest to disclose.
Preface

This document has been prepared by the Winnipeg Regional Health Authority/CancerCare Manitoba (WRHA/CCMB) Oncology Pharmacotherapeutic (P&T) Subcommittee’s Systemic Therapy Summaries Working Group, as a means of disseminating drug information and formulary decisions made by the Subcommittee. The CCMB Provincial Pharmacy Program, Provincial Oncology Drug Program (PODP) and Clinical Practice Guidelines Initiative (CPGI) have contributed to the development of this summary.

Systemic Therapy Summaries (STS) are being developed for drugs/or indications where the P&T Subcommittee, based on scientific data, has accepted clinical benefit. The P&T Subcommittee Chair and the CPGI Lead/Advisory Panel Chair approve all STS documents.

The content of this STS was in large part adapted from the Formulary Addition Request submitted to the P&T Subcommittee by the CCMB Lymphoproliferative Disorders (LYMP) Disease Site Group (DSG), January 2014. This document will be reviewed, and updated as necessary, once in every twelve-month period; unless emerging evidence from scientific research dictates otherwise.

Purpose

This document is intended as a guide to facilitate the safe and effective clinical use of brentuximab vedotin in the treatment of relapsed/refractory anaplastic large cell lymphoma (ALCL).

For this purpose, it may be used by qualified and licensed healthcare practitioners involved with the care of oncology patients, which may include (but is not limited to): physicians, nurses, and pharmacists at CancerCare Manitoba, Community Cancer Programs Network (CCPN) sites and WRHA Community Oncology Program sites.

Disclaimer

Use of this document should not preclude the practitioner’s independent clinical judgment, nor should it replace consultation with the oncologist.

It is the responsibility of the practitioner to develop an individualized treatment plan for each patient under his/her care, and ideally this should take place within the context of a multidisciplinary team. The unique needs and preferences of the patient and the family should always be reflected in the plan of care.

This document is not a comprehensive drug monograph. Practitioners must refer to other sources for complete drug information.
Brentuximab Vedeotin for Relapsed/Refractory Anaplastic Large Cell Lymphoma

Protocol Code: LYMP – Brentuximab vedotin

Developed by: Lymphoproliferative Disorders Disease Site Group

Date of Presentation to P&T Subcommittee: January 21, 2014

Treatment Recommendation

The Lymphoproliferative Disorders DSG recommends brentuximab vedotin for patients with relapsed/refractory ALCL who meet the inclusion criteria (see below).

Treatment Intent

- Non-curative
- Improve progression-free survival (PFS) and overall survival (OS)

Rationale

Systemic ALCL is an aggressive subtype of T-cell lymphoma representing approximately 2-3% of all lymphoid neoplasms. With the exception of low to intermediate risk anaplastic lymphoma kinase (ALK)-positive patients, patients with ALCL have a poor prognosis when treated with conventional anthracycline-based front-line chemotherapy, and 40-65% of patients with ALCL develop recurrent disease. Standard first-line care involves CHOP (cyclophosphamide, adriamycin, vincristine, prednisone) chemotherapy regimen followed by possible consolidative autologous stem cell transplant (ASCT). For patients with relapsed/refractory disease, there is no standard of care and treatment options are limited.

ALCL is characterized by the uniform expression of CD30, a transmembrane cytokine receptor, consistently expressed at diagnosis as well as relapse. First generation anti-CD30 antibodies were ineffective. Brentuximab vedotin is an antibody-drug conjugate that selectively delivers monomethyl auristatin E (MMAE), an antimicrotubule agent, into CD30-expressing cells.

The efficacy of brentuximab vedotin was demonstrated in the phase II trial SGN035-0004. Currently available alternatives include paletrexate and romidespin, both of which have substantially lower complete and objective response rates than observed in the brentuximab vedotin trial.

Clinical Benefit (Level Ib Evidence see Appendix I)

A single-arm, phase II clinical trial enrolled 58 patients with ALCL who had relapsed or were refractory to their most recent therapy. Median age was 52 years (range, 14-76) and Eastern Cooperative Oncology Group (ECOG) performance scores were 0 to 1. All patients had received at least one prior treatment; 50% had refractory disease, and 25% had received prior ASCT. The primary endpoint, objective response rate, was 86%
(95% confidence interval [CI], 74.6 to 93.9) and the secondary endpoint, complete response rate, was 57% (95% CI, 43.2 to 69.8). Also notable was that PFS after brentuximab vedotin was longer than PFS following the patient’s most recent prior treatment (hazard ratio, 0.48; p = 0.001). This is highly unusual in a disease characterized by progressively shorter times between treatments in relapse. Updated analysis of study patients (median observation time of 22.8 months) revealed a median duration of objective response of 13.2 months (range 0.1 to 27.7 months).

Patient Population and Selection Criteria

Inclusion Criteria

- Systemic ALCL; AND
- Confirmed CD30 antigen positive; AND
- Relapsed or refractory to previous multi-agent chemotherapy; AND
- An ECOG performance status of less than or equal to 2

CCMB Formulary Status

1. Formulary definition
   - Restricted drug

2. Adjudication process
   - Complete “Restricted Drug Form-LYMP DSG – NON-HODGKIN’S LYMPHOMA” (J:\Pharmacy\FORMS)
   - Approval required by: Lymphoproliferative Disorders DSG Chair or Designate
   - Disease status must be reassessed every 4 cycles. Further renewal will be granted only if disease response is documented after initial assessment

Implementation and Safety Considerations

- Do not administer as an intravenous push or bolus.
- Do not mix with, or administer as an infusion with other medicinal products.
- A missed dose should be administered as soon as possible. Subsequent doses should not be administered less than 3 weeks apart.
- Baseline vital signs taken prior to initiation of brentuximab vedotin infusion.
### Treatment Regimen – Brentuximab vedotin

1 cycle = 21 days

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>CCMB Administrative Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brentuximab vedotin</td>
<td>1.8 mg/kg (maximum = 180 mg)</td>
<td>Intermittent infusion IV in 100 mL normal saline (NS) over 30 minutes; once every three weeks</td>
</tr>
</tbody>
</table>

### Pre-Medications and Supportive Care

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>CCMB Administrative Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>650 mg</td>
<td>Orally, 30 minutes prior to brentuximab vedotin</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>50 mg</td>
<td>Orally, 30 minutes prior to brentuximab vedotin</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>12 mg</td>
<td>Orally, 30 minutes prior to brentuximab vedotin (may be given intravenously if indicated)</td>
</tr>
</tbody>
</table>
Clinical Monitoring and Follow-Up Recommendations

Hematology, chemistry and required tests

- Prior to each treatment:
  - Absolute neutrophil count (ANC) greater than or equal to $1 \times 10^9/L$ and platelets greater than or equal to $50 \times 10^9/L$

- During each cycle:
  - Complete blood count (CBC)

Clinical toxicity assessment

- During each cycle: Infusion-related hypersensitivity reaction symptoms (chills, nausea, cough and itching) may occur within 2 days after administration
  - If infusion-related reactions occur: stop infusion and contact prescribing physician. Patient should be observed for 1 hour and discharged if vital signs stable
  - If no infusion-related reactions occur: no observation period required

- Post-treatment: Allopurinol will only be prescribed for patients at risk of tumour lysis syndrome (300 mg orally daily for 21 days – at physician’s discretion)

Assessment of treatment response

- Patient must have demonstrated response to initial response assessment (post cycle 4) for ongoing approval
### Common or Clinically Important Adverse Events*4,5
(RRefer to individual drug monographs for full details of adverse events)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
</table>
| **Infusion-related reactions**         | Infusion-related reactions reported in 12% of patients. Reactions may be immediate or delayed, with symptoms occurring within 2 days after administration. In the event of an infusion-related hypersensitivity reaction, administer the following drugs as warranted:  
1. Meperidine 25 mg IV prn for rigors  
2. Diphenhydramine 25-50 mg IV prn for urticaria or swelling  
3. Dexamethasone 20 mg IV prn for stridor, new wheezing or patient complaining of difficulty breathing. |
| **Anemia**                             | Grade 3 or 4 anemia is reported in 33-52% of patients (2-10% severe) |
| **Neutropenia**                        | Neutropenia is reported in 54-55% of patients (21% severe)  
Anemia can be prolonged (greater than or equal to 1 week) |
| **Thrombocytopenia**                   | Thrombocytopenia is reported in 16-28% of patients (10% severe)  
Thrombocytopenia can be prolonged (greater than or equal to 1 week) |
| **Peripheral neuropathy**              | Peripheral sensory neuropathy is reported in 7-16% of patients (8-10% severe). Peripheral neuropathy is usually sensory in nature, but motor neuropathy has also been reported.  
Peripheral neuropathy is dose-cumulative, and usually occurs several months into therapy. Improvement or resolution of symptoms usually takes approximately 7 weeks. Most patients will have residual neuropathy symptoms. |
| **Progressive multifocal leukoencephalopathy (PML)** | PML is reported in less than 1% of patients, but specifically in patients following active John Cunningham virus infections, immunosuppressive therapies or underlying immunosuppressive disease |
| **Pancreatitis**                      | Acute pancreatitis, including fatal outcomes, have been reported. Consider the diagnosis of acute pancreatitis for patients presenting with new or worsening abdominal pain |
| **Dermatological**                    | Stevens-Johnson syndrome and toxic epidermal necrolysis, including fatal outcomes have been reported |

* See Appendix III CTCAE v.4.0
## Precautions

<table>
<thead>
<tr>
<th>Breastfeeding</th>
<th>Not recommended due to the potential secretion into breast milk.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>FDA Pregnancy Category D. Positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective). In an animal model, brentuximab vedotin has been shown to cross the placenta, causing embryo-fetal toxicities including early resorption, post-implantation loss, decreased numbers of live fetuses and external malformations (i.e., umbilical hernias and malrotated hindlimbs). For women of childbearing potential, use of two contraceptive methods is recommended during treatment.</td>
</tr>
<tr>
<td>Fertility</td>
<td>In an animal model, brentuximab vedotin caused potentially reversible, dose-dependent testicular toxicity.</td>
</tr>
<tr>
<td>Mutagenicity</td>
<td>Not mutagenic in Ames test or mammalian <em>in vitro</em> mutation test. Brentuximab vedotin is clastogenic in mammalian <em>in vivo</em> chromosome tests.</td>
</tr>
<tr>
<td>Contraindications</td>
<td>History of hypersensitivity reaction to brentuximab vedotin or Chinese hamster ovary cell proteins. Concurrent therapy with bleomycin (due to increased risk of pulmonary toxicity, bleomycin must be discontinued prior to beginning brentuximab vedotin treatment. Patients with a diagnosis of progressive PML or a history of PML.</td>
</tr>
</tbody>
</table>
### Dose Modifications[^4,^5]

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>PML</td>
<td>Brentuximab vedotin should be held if PML is suspected, and discontinued permanently if diagnosis is confirmed</td>
</tr>
</tbody>
</table>
| Myelosuppression           | Cycle length – modify according to protocol by which patient is being treated; if no guidelines are available then the following have been suggested:  
  - For Grade 3 or 4 neutropenia: hold dose until resolution to baseline or Grade 2 or lower; consider filgrastim support for subsequent cycles  
  - For recurrent Grade 4 neutropenia despite filgrastim support: discontinue or reduce dose to 1.2 mg/kg  
  - For Grade 3 or 4 thrombocytopenia: consider platelet transfusion or dose delay |
| Severe renal insufficiency  | Starting dose should be 1.2 mg/kg and patients should be closely monitored for adverse reactions |
| Hepatic insufficiency      | Starting dose should be 1.2 mg/kg and patients should be closely monitored for adverse reactions |
| Acute pancreatitis         | Hold brentuximab vedotin for any suspected case of acute pancreatitis and discontinue if acute pancreatitis is confirmed |
| Stevens-Johnson syndrome   | Discontinue brentuximab vedotin and administer appropriate medical therapy |
| and toxic epidermal necrolysis |                                                                                   |
| Severe peripheral neuropathy | For new or worsening Grade 2 or 3 neuropathy, hold brentuximab vedotin until neuropathy improves to Grade 1 or baseline, then restart at 1.2 mg/kg  
  For Grade 4 neuropathy, discontinue treatment |

[^4]: Effective: January 2014

[^5]: Updated: April 2015
### Drug Interactions

<table>
<thead>
<tr>
<th>Drug-drug interactions</th>
<th>CYP 3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir) - increased area under the curve (AUC) of MMAE by 34%. Monitor closely for adverse reactions.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CYP 3A4 inducers (e.g., dexamethasone, carbamazepine, phenobarbital, St. John’s Wort) - decreased AUC of MMAE by 46%. Avoid concurrent therapy if possible.</td>
</tr>
<tr>
<td></td>
<td>P-glycoprotein inhibitors (e.g., quinidine, verapamil, cyclosporine) - increased AUC of MMAE. Monitor closely for adverse reactions.</td>
</tr>
<tr>
<td></td>
<td>Blemycin - increased risk of pulmonary toxicity.</td>
</tr>
<tr>
<td>Drug-food interactions</td>
<td>Fruit or juice from grapefruit, Seville oranges, pomegranate or starfruit - act as CYP 3A4 inhibitors. Increase AUC of MMAE by 34%. Monitor closely for adverse reactions.</td>
</tr>
</tbody>
</table>

### Clinical Considerations

- A missed dose should be administered as soon as possible. Subsequent doses should not be administered less than 3 weeks apart.
- Reconstitute each 50 mg vial with 10.5 mL of sterile water for injection to yield a single-use 5 mg/mL solution. Gently swirl the vial to aid dissolution; do not shake. After reconstitution, immediately add to an infusion bag containing at least 100 mL volume to achieve a final concentration of 0.4-1.8 mg/mL and use within 24 hours.
- Do not mix with, or administer as an infusion with, other medicinal products.
- Do not administer as an intravenous push or bolus.
References


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## Appendix I

### Levels of Evidence

<table>
<thead>
<tr>
<th>Evidence Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Evidence obtained from meta-analysis of randomised controlled trials</td>
</tr>
<tr>
<td>Ib</td>
<td>Evidence obtained from at least one randomised controlled trial</td>
</tr>
<tr>
<td>IIA</td>
<td>Evidence obtained from at least one well-designed controlled study without randomisation</td>
</tr>
<tr>
<td>IIB</td>
<td>Evidence obtained from at least one other type of well-designed, quasi-experimental study</td>
</tr>
<tr>
<td>III</td>
<td>Evidence obtained from well-designed, non-experimental descriptive studies, such as comparative studies, correlation studies and case studies</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities</td>
</tr>
</tbody>
</table>

Appendix II

ECOG Performance Status Scale

<table>
<thead>
<tr>
<th></th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease activities without restriction (Karnofsky 90-10)</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physical strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework or office work (Karnofsky 70-80)</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about greater than or equal to 50% of waking hours (Karnofsky 50-60)</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair greater than or equal to 50% of waking hours (Karnofsky 30-40)</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled, cannot carry on any self-care, totally confined to bed or chair (Karnofsky 10-20)</td>
</tr>
</tbody>
</table>

Appendix III

**Common Terminology Criteria for Adverse Events (CTCAE) version 4.0**

**Publish Date: 18 May 2009**

<table>
<thead>
<tr>
<th>Grades</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Life-threatening consequences; urgent intervention indicated.</td>
</tr>
<tr>
<td>Grade 5</td>
<td>Death related to AE.</td>
</tr>
</tbody>
</table>

A semi-colon indicates ‘or’ within the description of the grade. A single dash (-) indicates a grade is not available. Not all grades are appropriate for all AEs. Therefore, some AEs are listed with fewer than five options for grade selection.

**Grade 5**: Grade 5 (Death) is not appropriate for some AEs and therefore is not an option.

**Activities of Daily Living (ADL):**

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

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