Practice Guideline: Systemic Therapy Summary

Treatment of Chronic Lymphocytic Leukemia with Pentostatin, Cyclophosphamide and Rituximab (CLL – PCR)

Lymphoproliferative Disorders Disease Site Group

Effective: May 2012
Updated: September 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 Medical Director/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), May 2012. 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 pentostatin, cyclophosphamide and rituximab in the treatment of chronic lymphocytic leukemia.

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.
Treatment of Chronic Lymphocytic Leukemia with Pentostatin, Cyclophosphamide and Rituximab

Protocol Code: CLL – PCR

Developed by: Lymphoproliferative Disorders Disease Site Group

Date of Presentation to P&T Subcommittee: May 22, 2012

Treatment Recommendation

The Lymphoproliferative Disorders Disease Site Group (DSG) recommends treatment of chronic lymphocytic leukemia (CLL) with pentostatin, cyclophosphamide and rituximab (PCR) for patients who meet the inclusion criteria (see below).

Treatment Intent

- Disease control in a heavily pretreated patient population that has failed previous purine analogue treatment (to minimize myelosuppression and infection risk)

Rationale

Pentostatin, also known as 2'-deoxycoformycin (DCF), is a purine analogue that is a potent inhibitor of adenosine deaminase. This enzyme is found in cells of the lymphoid system. By inhibiting adenosine deaminase, DNA and RNA synthesis are inhibited.¹

Pentostatin is considered to be the least myelosuppressive purine analogue and thus useful in the setting of combination therapy with cyclophosphamide in a heavily pretreated population. A pilot study of 23 patients demonstrated efficacy in the pentostatin and cyclophosphamide combination with 17 (74%) responses (4 complete responses (CR)). Given that the addition of anti-CD20 therapy has been shown to be more effective than the use of chemotherapy alone, PCR was developed.

Clinical Benefit² (Level IIb Evidence see Appendix I)

Lamanna and colleagues conducted a phase II single-arm trial where patients with CLL (n = 32) or other low-grade B cell neoplasms (n = 14) were treated with pentostatin (4 mg/m²), cyclophosphamide (600 mg/m²) and rituximab (375 mg/m²), for six cycles at 3-week intervals. For the CLL patients, there were 24 responses (75%); 8 complete responses (25%), 1 nodular response (3%) and 15 partial responses (47%). Overall, 28% of patients had Grade 3 or 4 infections.
Patient Population and Selection Criteria

Inclusion criteria

- Have CLL; **AND**
- Disease relapse after previous allogeneic stem cell transplant (ASCT) for CLL or not a candidate for stem cell transplant; **AND**
- Prior treatment with fludarabine-based therapy; **AND**
- Fludarabine-refractory disease (defined as less than a partial response to fludarabine-based therapy, or disease progression within 6 months of most recent fludarabine dose); **AND**
- Is not eligible for a clinical trial or a novel oral targeted agent; **AND**
- Confirmed CD20 antigen positive disease; **AND**
- An Eastern Cooperative Oncology Group (ECOG) performance status less than or equal to 2; **AND**
- Alemtuzumab-refractory disease (defined as disease progression during alemtuzumab-based therapy, or disease progression within 6 months of completion of alemtuzumab-based therapy); **OR**
- A contraindication to alemtuzumab-based therapy (e.g., bulky lymphadenopathy)

Exclusion criteria

- Pregnant patients
- Creatinine clearance (CrCl) less than 60 mL/minute
- Active infection

CCMB Formulary Status

1. Formulary definition
   - Restricted

2. Adjudication process
   - Complete “Restricted Drug Form-LYMP DSG-CLL” (J:\Pharmacy\FORMS); **AND**
   - Health Canada’s “Special Access Programme (SAP) Patient Specific Request”
   - Approval required by: Lymphoproliferative Disorders DSG Chair or Designate
   - Usual duration of approval: 6 cycles
Implementation and Safety Considerations

- Pentostatin may be administered at any CCP site.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>CCMB Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pentostatin</td>
<td>4 mg/m² on Day 1</td>
<td>IV in 50 mL normal saline (NS) over 30 minutes</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>600 mg/m² on Day 1</td>
<td>IV in 250 mL NS over 1 hour</td>
</tr>
<tr>
<td>Rituximab</td>
<td>375 mg/m² on Day 1</td>
<td>IV in NS 1 mg/mL final concentration (incremental rate of infusion) OR IV in 500 mL NS over 90 minutes (rapid infusion if no infusion related reactions with cycle #1)</td>
</tr>
</tbody>
</table>

**Treatment Regimen – CLL – PCR⁴,³**

1 cycle = 21 days
# Pre-Medications and Supportive Care

Drugs should be administered in the following order:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>CCMB Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine</td>
<td>50 mg on Day 1</td>
<td>Orally, 30 minutes prior to rituximab infusion</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>650 mg on Day 1</td>
<td>Orally, 30 minutes before rituximab infusion</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>12 mg on Day 1 (For Cycle #1, usually 20 mg pre-rituximab for high risk patients**)</td>
<td>IV in 50 mL NS over 15 minutes; 30 minutes before chemotherapy</td>
</tr>
<tr>
<td>Rituximab</td>
<td>(See above)</td>
<td>(See above)</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>8 mg on Day 1</td>
<td>Orally, 30 minutes before chemotherapy</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>(See above)</td>
<td>(See above)</td>
</tr>
<tr>
<td>Normal saline 0.9%</td>
<td>500 mL on Day 1</td>
<td>IV over 1 hour</td>
</tr>
<tr>
<td>Pentostatin</td>
<td>(See above)</td>
<td>(See above)</td>
</tr>
<tr>
<td>Normal saline 0.9%</td>
<td>500 mL on Day 1</td>
<td>IV over 1 hour; given post-pentostatin (post-hydration)</td>
</tr>
</tbody>
</table>

**High risk patients for hypersensitivity reaction – Administer dexamethasone 20 mg for patients who have: a history of previous anaphylactic or anaphylactoid episodes or; greater than $25 \times 10^9$/L of circulating malignant CD20 B-cells or; a high tumour burden, lesions greater than 10 cm in size or; current treatment with an ACE inhibitor (bradykinin release)
Clinical Monitoring and Follow-Up Recommendations

Hematology, chemistry and required tests

- Prior to each cycle:
  - Complete blood count (CBC) and serum creatinine

Assessment of treatment response

- If there is no response after 2 cycles of PCR, discontinue treatment
- Response will be assessed by clinical parameters

Common or Clinically Important Adverse Events*2
(Refer to individual drug monographs for full details of adverse events)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myelosuppression</td>
<td>Myelosuppression was the most frequent toxicity with Grade 3/4 neutropenia occurring in 53% of patients, Grade 3/4 thrombocytopenia in 16% of patients and Grade 3/4 anemia occurring in 9% of patients. Grade 3/4 infections (including fever of unknown origin) occurred in 28% of patients (mostly pneumonias)</td>
</tr>
<tr>
<td>Other</td>
<td>The only other Grade 3/4 toxicity reported was a single event of Grade 3 nausea (without vomiting)</td>
</tr>
</tbody>
</table>

* See Appendix III CTCAE v.4.0

Precautions1

<table>
<thead>
<tr>
<th>Condition</th>
<th>Precaution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system toxicities</td>
<td>If patients exhibit evidence of nervous system toxicity (i.e., lethargy, seizures, coma), withhold or discontinue therapy.</td>
</tr>
<tr>
<td>Skin reactions</td>
<td>If a patient experiences a severe rash, withhold therapy.</td>
</tr>
<tr>
<td>Infections</td>
<td>In patients with an active underlying infection, withhold therapy. Resume therapy once infection is controlled.</td>
</tr>
</tbody>
</table>

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Dose Modifications\(^1\)

There is insufficient data to recommend an initial or subsequent dose of pentostatin in patients with impaired renal function (i.e., CrCl less than 60 mL/minute).

No dosage adjustments necessary when starting therapy in patients with anemia, neutropenia or thrombocytopenia.

Drug Interactions\(^1\)

| Drug-drug interactions | Allopurinol and pentostatin | - associated with skin rashes. If a skin rash develops, then the prescriber should discontinue allopurinol. If the rash does not resolve after stopping the allopurinol, then the pentostatin should be discontinued. |
| | Fludarabine | - concomitant therapy with fludarabine is not recommended due to possible severe and fatal pulmonary toxicity (i.e., pneumonitis). |

Clinical Considerations\(^1,3\)

It is recommended that patients receive hydration with 500 to 1000 mL of 5% dextrose in water (D5W) with 0.45% NaCl injection, or a similar fluid prior to pentostatin administration. It is also recommended to hydrate with an additional 500 mL of D5W and 0.45% NaCl, or similar IV fluid immediately after pentostatin administration to minimize risk of adverse renal effects.

In patients with renal impairment (i.e., CrCl less than 60L/minute), the half-life increases to approximately 18 hours.

Patients should receive *Pneumocystis jiroveci* and herpes zoster prophylaxis. Patients should also receive filgrastim beginning Day 3 and continue daily until ANC greater than 1.5 \(X\) \(10^9\)/L for 2 consecutive days as primary prophylaxis.
References

   http://www.drugs.com/monograph/nipent.html


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### Appendix I

#### Levels of Evidence

<table>
<thead>
<tr>
<th>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>Grade</th>
<th>Description</th>
<th>Karnofsky Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease activities without restriction (Karnofsky 90-100)</td>
<td>90-100</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>
<td>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>
<td>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>
<td>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>
<td>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.
