WRHA/CCMB Oncology Pharmacotherapeutic (P & T) Subcommittee
Systemic Therapy Summary
Review/Update

STS Title: First-Line Palliative Treatment of Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma with Cetuximab, Platinum, and 5 FU
Protocol Code: Head & Neck – Cetuximab, Platinum, and 5 FU
Effective: September 2011
Annual Review: April 2014

The above-named CancerCare Manitoba Practice Guideline was under review for the following reason(s) – Please check all applicable:

☐ New evidence exists which affects the recommendation statement(s) and/or clinical content of the guideline
☐ New information exists which necessitates change in other content
☐ The guideline is no longer applicable and is to be retired from use
☑ The guideline is due for review as per P&T Subcommittee protocol
☐ Other

The DSG Chair and/or designated DSG member(s) have reviewed the content of the STS “First-Line Palliative Treatment of Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma with Cetuximab, Platinum, and 5 FU”. Any modifications to the document subsequent to DSG review have been discussed by the P&T Subcommittee STS Working Group.

Review of this CCMB Systemic Therapy Summary is now complete. The updated version is approved for re-distribution and clinical application according to policies and procedures as CCMB, WRHA Community Oncology sites, and Community Cancer Programs Network sites. The next scheduled date of review is: April 2014.

Approved by:

[Signature]
DSG Chair/Designate

[Date]
April 9/12

[Signature]
Dr. Ralph PW Wong, BSc, MD, FRCPC
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Pharmacotherapeutic Subcommittee

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March 11, 2013

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CCMB Clinical Practice Guidelines Initiative

[Date]
6 June 2013

cc. WRHA/CCMB Oncology P&T Subcommittee
Systemic Therapy Summaries Working Group
Associated Program Directors/Department Heads
Practice Guideline: Systemic Therapy Summary

First-Line Palliative Treatment of Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma with Cetuximab, Platinum, and 5 FU

(Head & Neck - Cetuximab, Platinum, and 5 FU)

Effective: September 2011
Required Update: April 2014
Annual Review: April 2013

CCMB Electronic Posting Date:
ACKNOWLEDGEMENT AND SPONSORSHIP DISCLAIMERS
Introduction

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 clinical benefit has been accepted by the P&T Subcommittee, based on scientific data. All STS documents are approved by the P&T Subcommittee Chair and the CPGI Lead/Advisory Panel Chair.

The content of this STS was in large part adapted from the Formulary Addition Request submitted to the P&T Subcommittee by the CCMB Gastro-Intestinal (GI) Disease Site Group, May, 2010. 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 cetuximab, platinum, and 5 FU in first-line palliative treatment of recurrent/metastatic head and neck squamous cell carcinoma.

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.
First-Line Palliative Treatment of Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma with Cetuximab, Platinum, and 5 FU

Protocol Code: Head & Neck - Cetuximab, Platinum, and 5 FU

Developed by: Head and Neck Disease Site Group

Date of Presentation to P&T Subcommittee: September 2011

Treatment Recommendation

Cetuximab, Platinum, and 5 FU is the preferred palliative treatment for patients with recurrent or metastatic head and neck squamous cell carcinoma.

Rationale

Recurrent or metastatic squamous cell carcinoma of the head and neck is managed with systemic therapy. The current standard is platinum based chemotherapy. The addition of Cetuximab to cisplatin and 5 fluorouracil regimens has demonstrated improved response rates, progression free survival and overall survival.

Clinical Benefit (Level 1 Evidence see Appendix I)

A controlled study randomised 442 patients with untreated recurrent or metastatic squamous cell carcinoma of the head and neck to two groups; cisplatin (or carboplatin) with 5-fluorouracil with or without cetuximab. The addition of cetuximab to chemotherapy (cisplatin or carboplatin plus 5-fluorouracil) improved overall survival (10.1 months vs. 7.4 months, p = 0.04), progression-free survival (5.6 months vs. 3.3 months, p < 0.001) and response rate 36% vs. 20%, - < 0.001) compared to chemotherapy alone.1

Similarly a large meta-analysis of 17 randomised controlled trials showed improved progression free survival, overall survival and overall response rate in various advanced cancers. In sub-group analysis of three eligible RCTs of head and neck cancers, there was a significant improvement of PFS (0.63, 0.54 – 0.73), OS (0.78, 0.67 – 0.91), and ORR in the cetuximab group (1.57, 1.15 – 2.16). Two of the three eligible trials included patients with metastatic/recurrent disease.2
Patient Population and Selection Criteria

Inclusion Criteria
Patients with good performance status with recurrent/metastatic head and neck squamous cell carcinoma, cetuximab therapy along with platinum (cisplatin or carboplatin) and 5 FU based chemotherapy may be considered for palliative treatment

Exclusion Criteria
- Non squamous cell histology
- Poor ECOG performance status >2, with expected survival of less than 3 months
- Inadequate hematologic, renal, or hepatic function
- Surgery or irradiation within the previous 4 weeks

CCMB Formulary Status

1. Formulary definition
2. Adjudication process

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>CCMB Administration Guideline</th>
</tr>
</thead>
</table>
| Cetuximab | 400 mg/m² Day 1 | IV loading dose (IV over 120 minutes) for one dose  
- administer at least 1 hour before start of cytotoxic chemotherapy agents  
- continues until disease progression  
- observe patient for 1 hour after drug is administered |
### Treatment Regimen - cont’d

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>CCMB Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab</td>
<td>250 mg/m² weekly</td>
<td>IV (over 60 minutes) weekly starting on Day 8 of first cycle</td>
</tr>
<tr>
<td>Platinum Agent:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin</td>
<td>100 mg/m²</td>
<td>IV over 1 hour</td>
</tr>
<tr>
<td></td>
<td>or</td>
<td></td>
</tr>
<tr>
<td>Carboplatin</td>
<td>AUC 5 mg/mL/min</td>
<td>IV over 1 hour</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Day 1 and every 3 weeks for a maximum of 6 cycles</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>1000 mg/m² per day</td>
<td>given for 4 days every 3 weeks for a maximum of 6 cycles</td>
</tr>
</tbody>
</table>

### Premedications and Supportive Care

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>CCMB Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ondansetron and Dexamethasone</td>
<td>8 mg PO</td>
<td>30 minutes prior to cisplatin then every 12 hours for 48 hours</td>
</tr>
<tr>
<td>Optional: Aprepitant</td>
<td>125 mg PO Day 1</td>
<td>30 minutes pre-chemotherapy</td>
</tr>
<tr>
<td></td>
<td>and 80 mg PO Days 2, 3</td>
<td>once daily in the morning</td>
</tr>
</tbody>
</table>
### Premedications - cont’d

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine</td>
<td>50 mg PO</td>
<td>30 – 60 minutes prior to each cetuximab dose</td>
</tr>
</tbody>
</table>

Consider topical hydrocortisone lotion and oral minocycline as outpatient prescriptions to prevent acneiform rash (Level 4 Evidence – based on low rates of Grade 3-4 rash in Toronto).

If mild to moderate hypersensitivity reaction – *stop the drug and administer*:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>100 mg</td>
<td>IV</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>50 mg</td>
<td>IV</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>50 mg</td>
<td>IV</td>
</tr>
</tbody>
</table>

For subsequent doses administer, *prior to infusion*:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Route</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>100 mg</td>
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</tr>
<tr>
<td>Diphenhydramine</td>
<td>50 mg</td>
<td>IV</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>50 mg</td>
<td>IV</td>
</tr>
</tbody>
</table>
Clinical Monitoring and Follow-Up Recommendations

Laboratory Tests

- **Baseline**: CBC, lyles, BUN, Creat, AST, ALT, GGT and alk phos, Ca and Mg
- **Weekly**: CBC, electrolytes, including K, Ca, and Mg should be monitored prior to each infusion, and replace depleted electrolytes as appropriate
- **With each cycle of cisplatin or carboplatin, AST, ALT, GGT and Alk phos as well as renal function with BUN, and Creat should be assessed**

Clinical Considerations

Recommended treatment discontinuation/dose adjustment for toxicities:

- see pre-medication section re hypersensitivity reactions
- grade II acneiform rash consider early administration of topical steroids and oral minocycline

Assessment of treatment response

Patients should be assessed every two weeks by the attending physician prior to therapy, and have a nurse assessment on alternate weeks prior to therapy to ensure there is no grade 3 or 4 skin toxicity necessitating holding the drug

Dose Modifications

Patients with more than a grade 1 acneiform rash should be examined carefully before every treatment, and appropriate steroid and/or antibiotic therapy initiated early (grade II).

Dose modification of cisplatin and 5-fluorouracil due to renal dysfunction or myelosuppression as per other protocols.
References

CCMB Contributors

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Lead and Advisory Panel Chair, CCMB Clinical Practice Guidelines Initiative

We gratefully acknowledge the support of CancerCare Manitoba, and the CancerCare Manitoba Foundation.
The Provincial Oncology Clinical Practice Guidelines Initiative
## 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>Ila</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.
