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

STS Title: Primary Curative Therapy for Head and Neck Squamous Cell Carcinoma with Cetuximab in Combination with Radiation
Protocol Code: Head & Neck – Cetuximab with Radiation
Effective: September 2011
Annual Review: February 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☐ The guideline is no longer applicable and is to be retired from use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 “Primary Curative Therapy for Head and Neck Squamous Cell Carcinoma with Cetuximab in Combination with Radiation”. 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

[Signature]
Dr. Ralph PW Wong, BSc, MD, FRCPC
Chair, WRHA/CCMB
Pharmacotherapeutic Subcommittee

[Signature]
Dr. Piotr Czaykowski, BSc, MD, MSc, FRCPC
Lead and Steering Committee Chair,
CCMB Clinical Practice Guidelines Initiative

April 9/13
Date

May 21/13
Date

June 6/13
Date

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

Primary Curative Therapy for Head and Neck Squamous Cell Carcinoma with Cetuximab in Combination with Radiation

(Head & Neck - Cetuximab with Radiation)

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

CCMB Electronic Posting Date:
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 in combination with radiation as the primary curative therapy for 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.
Primary Curative Therapy for Head and Neck Squamous Cell Carcinoma with Cetuximab in Combination with Radiation

Protocol Code: Head & Neck - Cetuximab with Radiation

Developed by: Head and Neck Disease Site Group

Date of Presentation to P&T Subcommittee: September 2011

Treatment Recommendation

Patients with locally advanced (non-metastatic) stage III or IV SCC of the head and neck with potential for cure with primary concurrent platinum based chemotherapy and radiotherapy but with contraindications to platinum chemotherapy use should be considered for concurrent therapy with Cetuximab and radiation therapy.

Treatment Intent

Primary curative therapy for patients with head and neck squamous cell carcinoma.

Rationale

The current standard of treatment for locally advanced squamous cell carcinoma of the head and neck is platinum based chemo radiotherapy. However for patients over the age of 70 and/or who cannot medically tolerate platinum based chemotherapy, radiation with concurrent Cetuximab has shown to improve overall survival, progression free survival and local recurrence rates.

Clinical Benefit (Level 1 Evidence see Appendix I)

A randomized control trial of 424 patients with locally advanced squamous cell carcinoma of the head and neck, compared radiation with Cetuximab to radiotherapy alone. Overall survival, progression free survival and loco-regional control were all improved in the combination treatment arm. The median overall survival was 49 months vs. 29.3 months in the combination therapy vs. radiation alone respectively (95% CI; 0.57 – 0.97, p = 0.03). Likewise the progression free survival median compared at 17.1 months vs. 12.4 months (95% CI; 0.54 – 0.90, p = 0.006), and the median loco regional control duration was 24.4 months vs. 14.9 months for combination therapy vs. radiation alone respectively.¹
Similarly a large meta-analysis of 17 randomized 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 the 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).²

### Patient Population and Selection Criteria

#### Exclusion Criteria
- Locally advanced (non metastatic) squamous cell carcinoma with no contraindications to platinum therapy
- Non squamous cell histology
- Poor performance status patients with expected survival of less than 3 months

### CCMB Formulary Status

1. Formulary definition
2. Adjudication process

#### Treatment Regimen: Head & Neck – Cetuximab and Radiation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>CCMB Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab</td>
<td>400 mg/m² Day 1</td>
<td>IV loading dose (IV over 120 minutes) for one dose starting at Day minus 7 from radiation start date, followed by</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>250 mg/m²</td>
<td>IV (over 60 minutes) weekly starting on Day 1; complete infusion 1 hour before radiation; observe patient for 1 hour after drug administered</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>Diphenhydramine</td>
<td>50 mg PO</td>
<td>30 – 60 minutes prior to each cetuximab dose</td>
</tr>
</tbody>
</table>

Hydrocortisone cream and minocycline as outpatient prescriptions to help prevent acneiform rash (Level 4 Evidence – based on low rates of Grade 3-4 rash in Toronto with treatment up front for prevention).

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

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

Laboratory tests

- Baseline: basic CBC, lytes, Ca and Mg
- Weekly: CBC, electrolytes, including K, Ca, and Mg should be monitored prior to each infusion, and replace depleted electrolytes as appropriate

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 or oral minocycline and steroids as toxicity with radiotherapy can impair ability to complete the course

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

If there is insufficient time available to administer Cetuximab prior to radiation by one week, start without a loading dose on the first day of therapy with the maintenance dose

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)
References

CCMB Contributors

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Approved By
Dr. Ralph PW Wong, Medical Oncologist
Chair, WRHA/CCMB Oncology Pharmacotherapeutic Subcommittee

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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

<table>
<thead>
<tr>
<th>Levels of Evidence</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>Score</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.
