London Health Sciences Centre
London Regional Cancer Program

Use of Cetuximab in Advanced Colorectal Cancer

GI Practice Guideline

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Table of Contents

1.0 PREAMBLE
1.1 Biology 3
1.2 Clinical trials in advanced colorectal cancer: efficacy 3
1.3 Adverse Events 4

2.0 ELIGIBILITY AT THE LRCP
2.1 Inclusion Criteria 6
2.2 Exclusion Criteria 7
2.3 Caution 7

3.0 REGIMENS SUPPORTED AT THE LRCP 7

4.0 TOXICITY MANAGEMENT 7

5.0 LOGISTICS
5.1 Administration 7

6.0 IMPACT 8

7.0 COSTS AND ACQUISITON PROCESS 9

References 9

Contact Information 10

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1.0 PREAMBLE

1.1 Biology

Cetuximab, approved by Health Canada for use in colorectal cancer is a chimeric monoclonal antibody, which targets epidermal growth factor (EGFR) by selectively blocking natural ligands, thereby preventing activation of signal transduction pathways, which have major roles in cancer cell proliferation, angiogenesis, metastasis, and inhibition of apoptosis. Antibody dependant cell cytotoxicity is also a mechanism of action with Cetuximab.

1.2 Clinical Trials in Advanced Colorectal Cancer: Efficacy

Studies have been conducted in the use of Cetuximab: 1) in combination with other chemotherapy as first-line treatment of advanced colorectal cancer; 2) as monotherapy for patients who have failed chemotherapy; and 3) in combination with other chemotherapy in patients who have failed first line therapy.
The chart below from the CCO PGI 2-27 (in draft) outlines the current studies with respect to the last two categories. In addition, two studies have been recently reported by news release alone (the NCIC CTG study of Erbitux vs. best supportive care, and the EPIC study comparing Irinotecan alone to Irinotecan plus Erbitux).

The studies below demonstrate an 8.8% to 12% response rate to Cetuximab as a single agent. The informal communications regarding the NCIC study of 572 chemotherapy resistant patients showed a statistacally significant improvement in overall survival.

The study by Cunningham (2004) suggests improved response for chemotherapy resistant patients treated with Irinotecan plus Cetuximab. The EPIC trial, which was similar, favoured the combination arm as well (although the primary endpoint of overall survival was not met in that study as it was in the Cunningham study). The study by Jennis (2005) suggests benefit from adding Cetuximab to FOLFOX-4.

In addition, we anticipate CO17, Cetuximab vs. Best Supportive Care, to be a positive trial, though final results await ASCO 2007.

Table 1. Clinical trials of Cetuximab in second-line or greater treatment of advanced colorectal cancer.

Author (reference)	Treatment	Treatment Failed Prior to Study	Evaluable Patients	Median Overall Survival (months)	Median Progression-free Survival (months)	Tumour Response
Cetuximab monotherapy						
Saltz 2004 (14)	CET	CPT-11	57	6.4	1.4	8.8%
Mirtsching 2004‡ (15)	CET	Fluoropyrimidines, CPT-11, OXAL	28	NR	2.4	11%
Lenz 2005‡ (16)	CET	Fluoropyrimidines, CPT-11, OXAL	346	6.6	NR	12%
Cetuximab combination therapy						
Cunningham 2004 (13)	CET+CPT-11 CET	CPT-11	218 111	8.6 6.9	4.1* 1.5*	22.9%* 10.8%*
Saltz 2005‡ (17)	CET+BEV+CPT-11 CET+BEV	CPT-11	76 total	NR	5.8 4.0	35% 23%
Jennis 2005‡ (18)	CET+FOLFOX-4 FOLFOX-4	CPT-11	50 52	NR	4.4 4.1	26%† 10%†
Saltz 2001‡ (19)	CET+CPT-11	IFL	121	NR	NR	17%
Herrero 2005‡ (20)	CET+CPT-11	CPT-11, OXAL	22	NR	NR	27%
Grothe 2005‡ (21)	CET+CAPOX	5FU, CPT-11, OXAL	15	5.5+	2.5	27%

Notes: CET, cetuximab; CPT-11, irinotecan; OXAL, oxaliplatin; NR, not reported; FOLFOX, 5FU + FA + oxaliplatin; BEV, bevacizumab; IFL, bolus 5FU/FA plus irinotecan; CAPOX, oxaliplatin plus capecitabine.
* Difference between groups is statistically significant, $p<0.05$.
† Based on preliminary data of 74 patients.
‡ Published in abstract form only.

1.3 Adverse Events

While data regarding adverse events is not yet available on the NCIC or EPIC studies, toxicities are outlined from the CCO PGI draft monograph:

Table 2. Toxicity documented in clinical trials of Cetuximab in the treatment of advanced colorectal cancer.

Author (reference)	Treatment	Evaluable Patients	Acne-like rash (%)		Grade 3/4 Hypersensitivity reactions (%)
			Any	Grade 3	
Cetuximab monotherapy					
Saltz 2004 (14)	CET	57	86	18	5.3
Mirtsching 2004* (15)	CET	29	NR	3.4	3.4
Lenz 2005* (16)	CET	346	90	6	2.3
Spitzer 2005* (22)	CET	743	69	5.5	2.4
Cetuximab combination therapy					
Schoffski 2002* (7)	CET+FOLFIRI	13	100	15.4	NR
Rougier 2004* (8)	CET+FOLFIRI	42	59.6	4.8	4.3†
Rosenberg 2002* (9)	CET+IFL	27	96.3	19	0
Tabernero 2004* (10)	CET+FOLFOX-4	20	NR	NR	0
Diaz Rubio 2005* (11)	CET+FOLFOX-4	43	NR	30.2	NR
Seufferlein 2005* (12)	CET+FUFOX	48	NR	17	5
Scott 2005* (23)	CET+FOLFOX-6	26	NR	12	4
Cunningham 2004 (13)	CET+CPT-11 CET	218 111	80 80	9.4 5.2	0 3.5
Saltz 2005* (17,24)	CET+BEV+CPT-11 CET+BEV	34 31	NR‡ NR‡	18 19	0 0
Jennis 2005* (18), Badarinath 2004*(25)	CET+FOLFOX-4 FOLFOX-4	38 pooled	55	3	2.6
Saltz 2001* (19)	CET+CPT-11	121	61	8	3
Herrero 2005* (20)	CET+CPT-11	22	81	9	0
Grothe 2005* (21)	CET+CAPOX	15	NR	13.3	0
Sobrero (EPIC) 2005* (26)	CET+CPT-11	389	NR	NR	1

Notes: CET, cetuximab; FOLFIRI, infusional 5FU + FA + irinotecan; NR, not reported; IFL, bolus 5FU/FA plus irinotecan; FOLFOX, 5FU + FA + oxaliplatin; FUFOX, weekly infusional 5FU + FA + oxaliplatin; CPT-11, irinotecan; BEV, bevacizumab; CAPOX, oxaliplatin plus capecitabine.
* Published in abstract form only.
† Based on preliminary data of 23 patients.
‡ 65% grade 2/3 in irinotecan group, 64% grade 2/3 in no irinotecan group.

The most common toxicity is acne-like rash, occurring in 55% to 100% of patients. Some studies have identified rash as a factor predictive of longer survival.

Acute hypersensitivity reactions occurred in 0 to 5% of patients, and is a potentially life threatening complication. Patients are routinely pre-medicated with anti-histamines, and should be observed for at least one-hour post infusion.

Electrolyte depletion - should monitor periodically for hypomagnesemia, hypocalcemia and hypokalemia during treatment and up to 8 weeks following the completion of therapy.

Infusion reactions - add most reactions (90%) were associated with the first infusion despite prophylactic antihistamines, and occurred within the first hour but can occur with later reactions.

Pulmonary Toxicity - severe cases of interstitial lung disease (ILD),which was fatal in one case occured in 3 of 774 (<0.5%) of patients with advanced colorectal cancer. In the event of acute onset or worsening of pulmonary symptoms, therapy should be interupted and a prompt investigation of the symptoms should occur.

Table 3. Incidence of Adverse Events with Irinotecan (*from package insert*)

Adverse Reactions	With Irinotecan	Without Irinotecan
Acneiform Rash	88%	90%
Diarrhea	72%	25%
Nausea	55%	29%
Abdominal pain	45%	26%
Vomiting	41%	25%
Constipation	30%	26%
Headache	14%	26%

2.0 ELIGIBILITY AT THE LRCP

2.1 Inclusion Criteria

- Advanced colorectal cancer
- Resistant to first and second line chemotherapy with anti-thymidylates, Irinotecan and Oxaliplatin
- >first line chemotherapy

2.2 Exclusion Criteria

- Known hypersensitivity to any components of cetuximab
- Pregnant or lactating females (urine test confirmation required)
- Pediatric patients

2.3 Caution

- Safety and efficacy has not been studies in patients with hepatic impairment.
- Safety and efficacy has not been studied in renally impaired patients.

3.0 REGIMENS SUPPORTED AT THE LRCP

1. Irinotecan in the last tolerated dose schedule and amount plus Cetuximab: Cetuximab 400 mg/M^2 loading dose, then 250 mg/M^2 q1week.
2. Cetuximab as above as a single agent.
3. Folfiri Ref: ASCO Abstract 4000 Journal of Clinical Oncology, 2007 ASCO Annual Meeting Proceedings Part I Vol 25, No 18S (June 20 Supplement) 2007:4000 Randomized phase III study of irinotecan and 5-FU/FA with or without cetuximab in the first line treatment of patients with metastatic colorectal cancer. The CRYSTAL trail.

4.0 TOXICITY MANAGEMENT

The particular toxicities of Bevacizumab require attention to be paid to eligibility, informed consent, monitoring, treatment and dose adjustment/discontinuation. Minocycline and other anti-acne medications may be used for the skin reaction.

5.0 LOGISTICS

5.1 Administration

Cetuximab is still under the Special Access Program (SAP) and, therefore forms for Health Canada are requied and available through LRCP Pharmacy.

Cetuximab should be administered over 2 hours IV as a loading dose of 400 mg/M^2 followed by weekly infusions of 250 mg/M^2 until disease progression. Severe infusion reactions (bronchospasm, stridor, hoarseness, urticaria, hypotension, cardiac arrest) have been reported in ~3% of patients (~90% with the first infusion despite the use of prophylactic antihistamines).

Note: Although a 20 mg test dose was used in some studies, it did not reliably predict the risk of an infusion reaction, and is not recommended. In case of severe reaction, treatment should be stopped and permanently discontinued. Immediate treatment for anaphylactic/anaphylactoid reactions should be available during administration. Patients should be monitored for at least 1 hour following completion of infusion, or longer if a reaction occurs. Mild-to-moderate infusion reactions (chills, fever, dyspnea) are managed by slowing the infusion rate and administering antihistamines.

Premedication with antihistamines is recommended. The maximum infusion rate is 5 mL/minute. Administer through a low protein-binding 0.22-micrometer in-line filter. Flush the line at the end of infusion using 0.9% NaCl.

6.0 IMPACT

Estimates for the use of Cetuximab can be drawn from actual data for 2005-06 as shown below. It is anticipated that approximately 40% of such patients will become, or present as metastatic, and in a steady state situation one could expect this to be the proportion of patients who could be offered this drug. Since very few of the PUKs would likely be candidates, we could assume that about (543 x 0.4) or 200+ patients, of whom perhaps 5% could afford or have third party insurance to cover the cost for the drug. The impact, therefore, is unlikely to be more than 10-20 patients per year, outside of clinical trials until third party insurers, and patterns utilization take on a larger role.

Site Group	Site Sub-Group (based on ICD10 codes)	New Cases to Centre in Report Period	Seen by RAD	Seen by SYS	Seen by SUR	Seen by PO
	Small Intestine	37	2	37	1	0
	Colon	311	59	281	30	0
	Rectosigmoid Junction	16	10	14	4	0
	Rectum, Anus	179	160	149	21	1
	Primary Unknown	105	55	71	38	0
sum		**648**	**286**	**550**	**94**	**1**

In the original studies, the drug benefitted approximately 50% of patients with response or stabilization of disease, with a mean duration of less than 3 months. Given as a q 1 weekly schedule, over sixty minutes administration time, and continuing for 3 months, at most this amounts to 120 hours of administration per year (10 pts x 1 hours x 12 infusions), or 15 chair-days, at what appears to be an over-estimate in the assumptions. The administration fee of $250 per session, or $30,000 would offset this.

7.0 COSTS AND ACQUISITION PROCESS

The cost is $3.20/mg. 100mg vial - $320.00, 400mg - $1280.00.

Acquisition cost depends on patient's private drug plan. They will need to verify with their plan if the drug is covered.

REFERENCES

1. Saltz L, Rubin M, Hochster H. Tchekmeydian NS, Needle M, et al. Cetuximab (Imc-C225) plus irinotecan (CPT-11) is active in CPT-11-refractory colorectal cancer (CRC) that expresses epidermal growth factor receptor (EGFR). Proc Am Soc Clinical Oncology 2001, Abstract #7.

2. CCO PGI Evidence-based Series #2-27 Cetuximab (Erbitux®, C225) in the Treatment of Advanced Colorectal Cancer D Jonker, K Spithoff, RB Rumble, and the Gastrointestinal Cancer Disease Site Group **Report Date: May 10, 2006.**

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This guideline is a statement of consensus of the GI Disease Site Team regarding their views of currently accepted approaches to treatment. It is not intended to replace the independent medical judgement of the physician in the context of individual clinical circumstances to determine any patient's care or treatment.