Cetuximab in locally advanced head-and-neck cancer: defining the population

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ABSTRACT

Encouraging data for targeted therapy in head-and-neck squamous cell carcinoma are opening new options for treatment. Phase III trials of cetuximab, an antibody directed against the epidermal growth factor receptor (EGFR) have demonstrated benefit in the locally advanced and metastatic settings. Recognizing the importance of emerging therapies, Cancer Care Ontario published guideline recommendations for EGFR-targeted therapy in stage III and IV head-and-neck cancer. The present paper takes a further look at the population for whom an offer of cetuximab therapy may be appropriate.

KEY WORDS

Head-and-neck squamous cell carcinoma, locally advanced, cisplatin, cetuximab, radiotherapy

1. INTRODUCTION

Head-and-neck squamous cell carcinoma (HNSCC) is the sixth most common malignancy diagnosed worldwide and affects approximately 4600 Canadians annually. Encouraging data for targeted therapy in HNSCC are opening new options for treatment. Cetuximab, an antibody directed against the epidermal growth factor receptor (EGFR), has undergone the most clinical research, with phase III trials demonstrating benefits in the locally advanced and metastatic settings [1–3]. Recognizing the importance of emerging therapies, Cancer Care Ontario (CCO) published guideline recommendations for EGFR-targeted therapy in stage III and IV head-and-neck cancer in the June 2010 issue of *Current Oncology* [4].

2. DISCUSSION

2.1 CCO Evidence-Based Series

The CCO recommendations [4], developed in May 2009, state:

> Platinum-based chemoradiation remains the current standard of care for treatment of locally advanced HNSCC.
>
> In patients with locally advanced HNSCC who are medically unsuitable for concurrent platinum-based chemotherapy or who are over the age of 70 years (because concurrent chemotherapy does not appear to improve overall survival in this patient population), the addition of cetuximab to radical radiotherapy should be considered to improve overall survival, progression-free survival, and time to local recurrence.

As in the National Institute for Health and Clinical Excellence (NICE) guidelines, platinum ineligibility is emphasized; however, NICE also specifies a Karnofsky performance status (KPS) of 90% or better [5].

In May 2009, the Ministry of Health in Ontario reviewed the proposal and, under the New Drug Funding Program, approved cetuximab as combination therapy with radiotherapy for the initial treatment of locally or regionally advanced HNSCC with curative intent only for patients 70 years of age or older with a KPS of 90% or better.

2.2 British Columbia and Canadian Eligibility for Cetuximab Coverage

In British Columbia, cetuximab has been an approved therapy for combined-modality treatment since January 2008. The guidelines for use stipulate locally advanced stage III or IV HNSCC, an Eastern Cooperative Oncology Group performance status of 0–2, suitability for radical radiotherapy, and ineligibility for concurrent chemotherapy with cisplatin [6]. The BC Cancer Agency (BCCA) uses a practical definition for cisplatin ineligibility. It includes criteria typically used by clinical trials as absolute contraindications: a glomerular filtration rate below 50–60 mL/min and an inability to tolerate fluid load. Relative contraindications include neuropathy, risk of significant ototoxicity, comorbid disease, poor performance status, and age.

Selected provinces across Canada have approved cetuximab for use in HNSCC. In Alberta, cetuximab

is funded for a patient population similar to that in Ontario: cisplatin-ineligible patients 70 years of age or older with a good performance status may receive cetuximab concurrent with radiotherapy. In Quebec and Nova Scotia, the guidelines are similar to those in British Columbia: cetuximab is approved for locally advanced HNSCC in combination with radiation therapy for patients who have a contraindication to cisplatin chemotherapy. The participation of additional provinces is anticipated in 2010.

2.3 Defining the Population: Does the Updated Subgroup Analysis Help?

In the trial by Bonner *et al.* [1], patients with locally advanced HNSCC were randomized to high-dose radiotherapy alone or to high-dose radiotherapy plus weekly cetuximab. More than 400 patients were randomized, and the 5-year survival data confirm the initial benefit seen: median survival was 29.3 months compared with 49 months [hazard ratio (HR): 0.73; $p = 0.018$], with a 5-year overall survival of 36.3% and 45.6% respectively [2]. The updated publication included an analysis of the effect of cetuximab on survival in patient subgroups. Interestingly, oropharyngeal tumours, early T stage, advanced N stage, concomitant boost, high KPS (90%–100%), male sex, and age 65 years or younger were factors associated with a potential increase in benefit with cetuximab added to radiotherapy. This population is characteristic of human papilloma virus (HPV)–positive patients; however, the effect of HPV status is unknown because it was not evaluated in the trial.

In the Canadian landscape, eligibility for cetuximab has focused on two characteristics: age and performance status. Age was incorporated into provincial guidelines because the meta-analysis by Pignon *et al.* [7] of chemotherapy in HNSCC indicated that the HR for death with concomitant chemoradiotherapy was not better than that for locoregional treatment alone in patients 71 years of age and older. Therefore, in certain centres, elderly patients with locally advanced HNSCC are offered radiotherapy alone.

The relevant data must be tempered with the recognition that elderly patients represented only a small fraction (<8%) of the age subgroup analyzed. Moreover, in comparison to their younger counterparts, elderly patients maybe unable to complete treatment because of comorbid disease, and more of them die from other causes, making evaluation of the treatment effect difficult. Because outcomes with cetuximab and radiotherapy are superior to those with single-modality treatment, Ontario and Alberta have both opted to offer the combination option to the population 70 and older because of chemoradiotherapy unsuitability.

In the subgroup analysis of the Bonner data, the trend in patients aged 65 years and older favoured radiotherapy alone, and age less than 65 years was a factor associated with a potential increase in benefit from cetuximab. Again, interpretation of these data must be cautious, given the limited numbers and the increased competing mortality risk in older patients. Furthermore, the subgroup analysis was not powered to assess the data by age. Nonetheless, the forest plot suggests that cetuximab use provides greater benefit in younger than in older patients. Development of provincial policy is difficult; it requires a balance of evidence and cost implications. However, restricting cetuximab use to the 70 and older population denies younger platinum-ineligible patients a valid therapy.

Performance status has also been incorporated into several guidelines for cetuximab use. The United Kingdom's NICE, an independent organization that develops standards of health care based on up-to-date evidence and economic analysis, reviewed the use of cetuximab in locally advanced HNSCC [5]. After assessing the data in 2008, NICE requested a breakdown of survival data by KPS. For patients with KPS scores of 90% and 100%, that breakdown showed a survival HR of 0.61 [95% confidence interval (CI): 0.28 to 1.31] and 0.58 (95% CI: 0.39 to 0.88) respectively. For patients with a KPS score below 90%, the survival HR favoured radiotherapy alone. Based on that subgroup analysis and a consideration of the financial impact, NICE recommended the use of cetuximab for patients with locally advanced HNSCC whose KPS is 90% or better, and for whom platinum-based chemoradiotherapy is contraindicated. The decision to restrict therapy to patients with a good KPS was made based on a modest number ($n = 135$) of trial patients with poor KPS scores.

The updated subgroup analysis also highlighted benefit for cetuximab in other specific populations: oropharyngeal tumours, early T stage, advanced N stage, concomitant boost, and men. Unlike age and KPS, those features have not been used to select patients for therapy, even though the quality of the evidence is similar. In truth, the Bonner *et al.* study is a single trial assessing EGFR-directed therapy with radiation in locally advanced HNSCC, and conclusions regarding subgroup eligibility for therapy should be made only with great care.

The Bonner trial was never designed for platinum-ineligible patients; the objective of the authors was to evaluate cetuximab in a broad population of patients with stage III and IV HNSCC. Cetuximab therapy has been adopted into practice in Canada for patients who are platinum-ineligible or elderly because it offers an alternative that is recognized to be superior to radiotherapy alone.

2.4 B.C. Experience with Cetuximab: Patient Selection for Therapy

From January 2008 to February 2010, 85 patients were treated with cetuximab concurrent with radiotherapy at the 5 regional BCCA centres. Table I summarizes the baseline characteristics of the patients. Median

TABLE I Baseline patient characteristics

Characteristic	*Value*
Patients (*n*)	85
Sex (males/females)	72/13
Age (years)	
Median	62
Range	(40–89)
ECOG performance status (*n*)	
0	18
1	48
2	17
3	2
Patients ≥70 years (*n*)	26
Patients ≥70 years and performance status 0–1 (*n*)	21
Primary site of disease [*n* (%)]	
Oral cavity	12 (14)
Oropharynx	44 (52)
Hypopharynx	5 (6)
Larynx	14 (16)
Salivary gland SCC	2 (2)
Unknown	8 (10)

ECOG = Eastern Cooperative Oncology Group; SCC = squamous cell carcinoma.

age at diagnosis was 62 years, with 30% being over the age of 70; 78% had a performance status of 0 or 1; most had oropharyngeal primaries. Charts were reviewed to establish the reason or reasons for platinum ineligibility (Table II). As anticipated, the typical difficulties in administering cisplatin were found: ototoxicity, cardiac or vascular disease, renal insufficiency, marked weight loss, poor performance status, and neuropathy. Other factors that limit the deliverability of chemotherapy in general were also noted: hepatitis B or C, inadequate bone marrow reserve, recent surgery, or recent serious active infection. Age was a minor factor cited in 9 patients, 5 of whom were older than 80, and 5 of whom had other comorbid conditions that precluded the use of cisplatin. Performance status was a limiting factor in 4 patients; 2 had other indications for platinum ineligibility. Using the criteria of age 70 years or older, 59 of our 85 patients would have been excluded from cetuximab treatment, and 19 patients with a poor KPS score would not have been offered therapy.

3. WHERE DO WE GO FROM HERE?

It is clear that cetuximab offers a less-toxic and well-tolerated alterative to platinum-based chemotherapy for radiosensitization in locally advanced head-and-neck cancer. Given that no head-to-head comparisons of cetuximab and cisplatin with radiotherapy are available, it is impossible to determine whether these therapies offer an equivalent survival benefit to patients. The results of the HN6 trial, in which patients are being randomized to radiotherapy plus cisplatin or panitumumab (another EGFR-directed antibody), are eagerly awaited to help answer this question. The recently closed-to-accrual Radiation Therapy Oncology Group 0522 trial (randomization to radiotherapy and cisplatin or to radiotherapy, cisplatin, and cetuximab) will allow for an evaluation of the additive benefit of the antibody.

The Bonner trial update provides food for thought with respect to the population for whom an offer of cetuximab therapy is appropriate; however, restricting treatment on the basis of the *post hoc* subgroup analysis is unwise. The accessibility of cetuximab in Canada, albeit with limitations, offers selected patient populations an alternative treatment option for locally advanced HNSCC.

TABLE II Reason for cisplatin ineligibility and cetuximab use in British Columbia in 85 patients[a]

Reason	*Patients (n)*
Ototoxicity	25
Cardiac or vascular disease	19
Age	9
Poorly controlled psychiatric condition	8
Nephrotoxicity	7
Neurotoxicity	6
Poor glycemic control	6
Hepatitis B or C	5
Significant weight loss	5
Poor performance status	4
Active substance abuse	3
Inadequate bone marrow reserve	3
Recent surgery	2
Tracheostomy	2
Recent active infection	2

[a] Some patients had multiple comorbidities that limited the use of cisplatin.

4. REFERENCES

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