available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Review

Cetuximab combined with radiotherapy: An alternative to chemoradiotherapy for patients with locally advanced squamous cell carcinomas of the head and neck?

J. Bernier, D. Schneider*

Radio-Oncologie, Clinique de Genolier, Genolier 1272, Switzerland

ARTICLE INFO

Article history:
Received 22 August 2006
Received in revised form
23 August 2006
Accepted 24 August 2006
Available online 13 November 2006

Keywords:
Chemoradiotherapy
Cetuximab
Erbitux
Locally advanced
Radiotherapy
SCCHN

ABSTRACT

Radiotherapy remains the foundation of current treatment for patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN). It has been shown that the addition of concurrent chemotherapy to radiotherapy (chemoradiotherapy, CRT, or chemotherapy-enhanced radiation therapy, CERT) results in improved clinical outcome in terms of both locoregional control and overall survival in some groups of patients. However, CRT is associated with severe, dose-limiting acute toxicities and, in some patients, a higher proportion of late toxicities. In addition, most CRT regimens are platinum-based and there is evidence that the maximum tolerable toxicity has been reached with the dose intensities currently used in bolus cisplatin regimens. Therefore, if we are to further improve outcomes through increased treatment compliance, more effective and more tolerable regimens are needed. Recent results from a phase III randomised study demonstrate that the epidermal growth factor receptor (EGFR) inhibitor cetuximab (Erbitux®) given concomitantly with radiotherapy yields a significant clinical benefit over radiotherapy alone without any increase in radiotherapy-associated toxicity. In this review, we explore the question of the degree to which adding cetuximab improves the efficacy of radiotherapy in locally advanced SCCHN and how the benefits of cetuximab plus radiotherapy compare with those achievable with CRT.

1. Treatment rationale for SCCHN

Cancers of the head and neck, primarily squamous cell carcinomas of the oral cavity, pharynx and larynx, account for over 5% of all malignancies. Worldwide, in 2002, there were in excess of 500,000 new cases and over 300,000 deaths attributed to this disease.[1]

Surgery and/or radiotherapy are commonly used to treat locally advanced disease.[2] However, a considerable proportion of patients relapse, either locally or at distant sites, following surgery.[3] In addition, the long-term treatment outcome of patients with locally advanced disease is known to be poor with conventional schedules of radiotherapy: locoregional control of the disease is seen in approximately 30% of patients,[4,5] with 5-year survival rates of only 15%–25%[6] and median survival of approximately 12 months.[7] The general lack of success associated with the range of treatments available for locally advanced SCCHN prompted the search

* *Corresponding author:* Tel.: +41 919673803; fax: +41 918118678.
E-mail address: jacques.bernier@hcuge.ch (J. Bernier).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2006.08.035

for new approaches which resulted in the development of alternative radiotherapy fractionation schedules, such as hyperfractionation and accelerated fraction with concomitant boost,[8,9] both of which have been shown to be more effective in terms of locoregional control than standard fractionation in this setting.[10]

In parallel, strategies were developed to integrate the administration of systemic chemotherapy into radiotherapy schedules, with certain of these cytotoxic agents being used as radio-sensitisers.[5,11] The rationale for this approach was based both on increasing the tumour cell kill at the local level and additionally on targeting distant micro-metastases present at the time of the primary treatment.[12] This led to the implementation of high dose-intensity regimens, which resulted in significant increases in treatment efficacy, in terms of locoregional control and survival.[5,11] However, this increase in efficacy came at the cost of increased toxicity, particularly in relation to severe acute side-effects which were seen in a significant number of patients. Consequently, poor treatment compliance is observed in around one-third of cases, commonly in those receiving cisplatin (100 mg/m^2 every 3 weeks).[5,11]

Therefore, there was a clear need to optimise treatment combinations based on drug-radiotherapy interactions and to develop protocols integrating novel, highly efficient agents able to exert synergistic effects with radiotherapy as well as increasing its selectivity index.

2. The concept of cytotoxic enhancement

In addition to the systemic effects of cytotoxic chemotherapy, the concomitant administration of chemotherapy and radiotherapy capitalises on the radiosensitising properties of standard cytotoxic agents to improve locoregional control. Throughout the last two decades, three types of combination chemotherapy and radiotherapy – neoadjuvant, adjuvant and concurrent – have been compared with radiotherapy alone. Concurrent chemoradiotherapy (CRT), also known as chemotherapy-enhanced radiation therapy (CERT),[13] has been shown to be the most effective approach, with most studies showing significant increases at 3 years in both survival and locoregional control rates when CRT is compared with radiotherapy alone.[4,14–19]

Studies have shown a clinical benefit of CRT over radiotherapy in certain groups of patients with locally advanced disease. Most studies conducted to date have used radiotherapy together with cisplatin alone or in combination with 5-FU.[4,14,15,20–22] A phase III randomised, three-arm study reported by Adelstein et al. allowed for a direct comparison of two concomitant CRT regimens (radiotherapy versus radiotherapy plus concurrent bolus cisplatin versus split course of fractionated radiotherapy and concurrent infusional FU and bolus cisplatin) in 295 patients with unresectable disease.[14] The results from this trial demonstrated the superiority of single-agent cisplatin CRT over radiotherapy alone (3-year projected overall survival 37% versus 23%, $p = 0.014$). However, the use of split-course radiotherapy with combined chemotherapy was associated with a similar survival rate to radiotherapy alone (27%), but with a significant increase in $\geqslant$grade 3 toxicity. A potential reason for the lack of benefit with the multi-agent arm is the scheduling of the split-course radiotherapy, which was designed to allow for the possibility of mid-course surgery for any patients rendered resectable by the initial CRT. Split-course radiotherapy is generally recognised as a suboptimal way of delivering radiotherapy[23] and in this case was evidently not offset by either the multi-agent chemotherapy or the possibility of mid-course surgery.[14] Furthermore, treatment compliance was poorer in the CRT/split-course arm, with 27% of the patients failing to complete treatment compared with corresponding figures of 7% in the radiotherapy arm and 15% in the radiotherapy/cisplatin arm.

In a large phase III randomised study in 270 assessable patients, the addition of cisplatin/5-FU/FA to radiotherapy significantly improved 3-year overall survival (49% versus 24%, $p < 0.0003$) and 3-year locoregional control rate (35% versus 17%, $p < 0.004$) compared with radiotherapy alone.[4] Interestingly, the proportion of distant failures was similar in each arm (approximately 9%). Several smaller, but influential, studies have also shown the efficacy of radiotherapy combined with cisplatin/5-FU in unresectable disease. A phase III study compared the survival rates in 171 patients with previously untreated, unresectable oro- and hypo-pharyngeal carcinomas, randomised to receive CRT (3 cycles of cisplatin and 5-FU plus radiotherapy) or radiotherapy alone.[20] The addition of chemotherapy to radiotherapy significantly improved the overall survival rate at 18 months (48% versus 36%, $p = 0.05$), although these benefits were mainly confined to the 123 patients with oropharyngeal carcinoma, where the median survival time was prolonged from 10 to 17 months ($p < 0.05$). In another single-arm study in 50 patients, cisplatin and 5-FU were combined with hyperfractionated radiotherapy and compared with a historical control group of 29 patients who had received radiotherapy alone.[21] With a median follow-up of 23 months, the overall 2-year survival rates were 80% and 43% ($p < 0.01$), respectively.

The use of a different chemotherapy regimen, mitomycin C plus 5-FU, added to hyperfractionated accelerated radiotherapy (C-HART) was investigated in a large phase III randomised study in 384 patients with unresectable SCCHN.[24] The use of C-HART was associated with a 5% increase in the 5-year survival rate and a 13% increase in the 5-year locoregional control rate compared with HART alone.[24] Finally, a phase III randomised study in 350 patients with locally advanced nasopharyngeal carcinoma, which compared weekly concurrent cisplatin-enhanced radiotherapy to radiotherapy alone, demonstrated a significant advantage for the cisplatin-radiotherapy over radiotherapy alone with 5-year overall survival (OS) 70% versus 59%, respectively.[25]

3. Identifying the most effective CRT regimens

The benefits of CRT compared with radiotherapy alone in some patients with locally advanced disease have also been demonstrated by meta-analyses. The update of the Meta-analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) Collaborative Group's database[26] confirmed the findings of a previous, smaller analysis[27] and demonstrated a survival advantage for CRT of 5% at 5 years. This survival benefit was confined mainly to patients treated with chemotherapy administered concomitantly with radiotherapy: when data