Journal of Radiotherapy in Practice

Journal of Radiotherapy in Practice (2014)
13, 93–97 © Cambridge University Press 2013
doi:10.1017/S1460396912000532

Case Study

Response to concurrent cetuximab: radiotherapy following failure of platinum-based induction chemotherapy in squamous cell carcinoma of the larynx

L. Pettit, P. Ramachandra

Deansley Centre, Royal Wolverhampton Hospital, Wolverhampton, UK

(Received 14th July 2012; revised 6th September 2012; accepted 27th September 2012; first published online 22nd April 2013)

Abstract

Concurrent chemoradiation is the standard of care in the non-surgical management of locally advanced squamous cell carcinoma (SCC) of the larynx. Cetuximab can be used as an alternative to platinum for concomitant radiotherapy and the addition of cetuximab to cisplatin has been reported to improve response rates compared with cisplatin alone. We report two cases of patients who progressed through platinum-based induction chemotherapy and subsequently achieved a complete response with concurrent cetuximab radiotherapy.

Key words: cetuximab; chemoradiation; squamous cell carcinoma of the head and neck

INTRODUCTION

Concurrent chemoradiation is the standard of care in the non-surgical management of locally advanced squamous cell carcinoma (SCC) of the larynx. In addition to comparable cure rates with surgery, radiotherapy offers the prospect of laryngeal preservation; resulting in improved quality of life.[1,2] Larynx preservation rates of up to 84% at 3 years with platinum-based chemoradiation have been reported.[3]

Tumour response to platinum-based induction chemotherapy is frequently used as a selection criteria in clinical trials as a basis for deciding which patients proceed to definitive radiotherapy; with non-responders traditionally assigned to laryngectomy. The Groupe Oncologie Radiothérapie Tête et Cou (GORTEC) 2000–2001 trial demonstrated improved larynx preservation rate with the addition of docetaxel to cisplatin and 5-flurouricil (TPF) induction chemotherapy regime (3-year larynx preservation rates 70% TPF versus 58% PF).[4]

Cetuximab is an IgG1 chimeric monoclonal antibody directed against the epidermal growth factor (EGFR). Both over expression of EGFR and resistance to platinum confer a poor prognosis in SCCHN.[5] EGFR is thought to contribute to radioresistance by protecting cells from immediate radiation-induced DNA damage, and enabling cellular survival and repopulation via activation of downstream pathways such as mitogen-activated protein kinase (MAPK) pathways

Correspondence to: Dr Laura Pettit, Hall-Edwards Research Radiotherapy Group, Queen Elizabeth Hospital, Birmingham, UK. Tel: +44 (0) 7779089066. E-mail: l.pettit@nhs.net

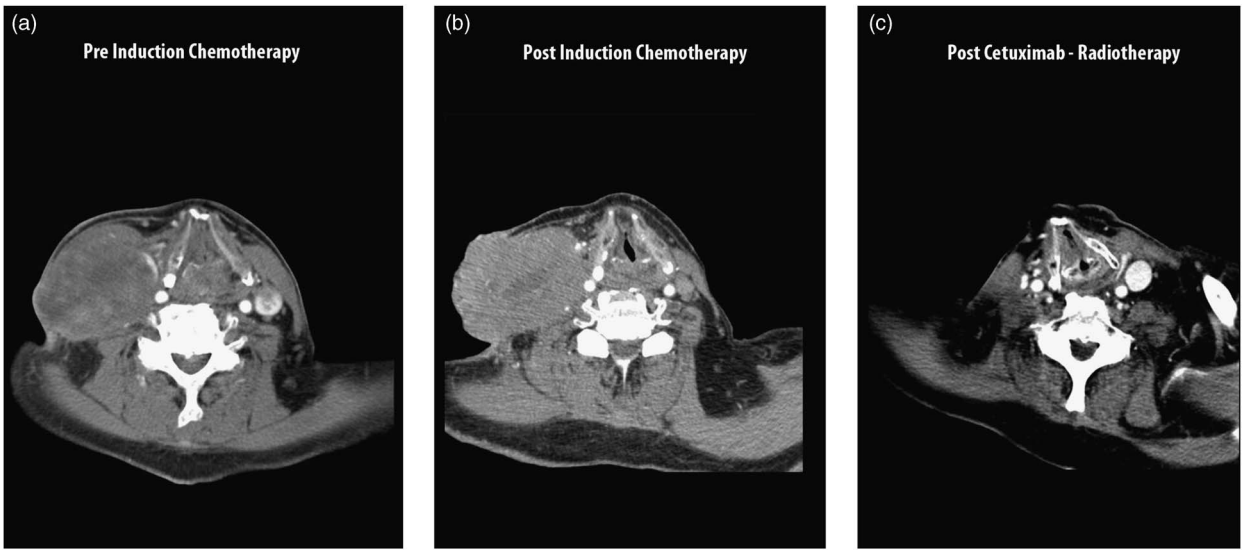

Figure 1. (a) Pre-induction chemotherapy; (b) Post-induction chemotherapy; (c) Post-cetuximab radiotherapy.

after radiotherapy. Radiotherapy increases expression of EGFR; blockade of EGFR signalling then sensitises cells to the effects of radiation.

Cetuximab can be used as an alternative to platinum for concomitant radiotherapy and the addition of cetuximab to cisplatin has been reported to improve response rates compared with cisplatin alone.[6,7]

We report two cases of patients who progressed through platinum-based induction chemotherapy and subsequently achieved a complete response with concurrent cetuximab radiotherapy.

CASE 1

A 65-year-old male presented in August 2010 with a right-sided neck mass. Clinically he had a 7×8 cm lymph node mass with associated oropharyngeal bleeding threatening complete respiratory obstruction, necessitating an emergency tracheotomy.

Nasendoscopy confirmed an extensive tumour arising from the right hypopharynx which appeared to involve the right aryepiglottic fold, lateral part of the epiglottis, lateral pharyngeal wall and lateral part of the posterior pharyngeal wall, with the upper limit below the right tonsil. Subsequent fine needle aspiration from the right neck node confirmed poorly differentiated SCC.

Computed tomography (CT) confirmed a right pyriform fossa/supraglottic primary with a large 6 cm fixed nodal mass invading the skin with extra capsule spread into the sternocleidomastoid muscle (see Figure 1a).

He was diagnosed with a rapidly progressing T3 N3 SCC of the hypopharynx. The neck mass was deemed inoperable and he subsequently received induction chemotherapy with cisplatin 75 mg/m^2 and 5FU 3000 mg/m^2 in attempt to render the tumour operable. Cycle 1 was given on 28th September 2010. Following cycle 2 on 19th October 2010 the tumour had progressed to 10 cm and was fungating through the skin surface (Figure 1b).

The third cycle of chemotherapy was abandoned. He was deemed not to be a surgical candidate and subsequently proceeded to radical radiotherapy 70 Gy in 35 fractions from 29th November 2010–14th January 2011 with concurrent weekly cetuximab – loading dose 400, 250 mg/m^2 weekly thereafter during radiotherapy. By week 3 the tumour mass had decreased to 6 cm and by week 7 it was not palpable. He had achieved a complete radiological response as evidenced by Figure 1c.

https://doi.org/10.1017/S1460396912000532 Published online by Cambridge University Press

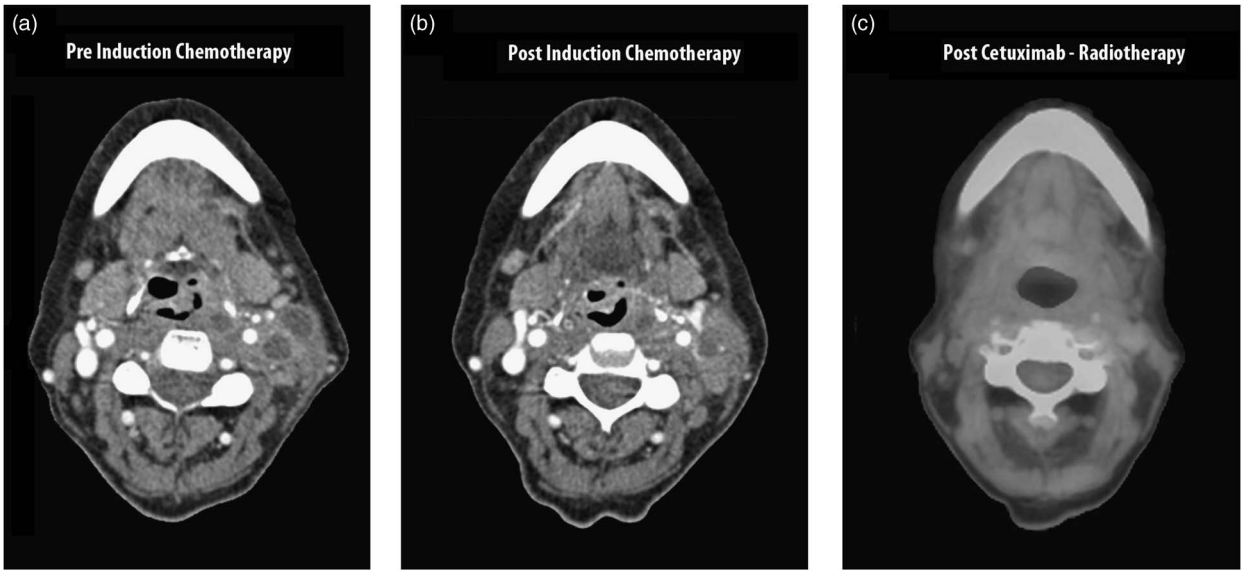

Figure 2. (a) Pre-induction chemotherapy; (b) Post-induction chemotherapy; (c) Post-cetuximab radiotherapy.

CASE 2

A 64-year-old female heavy smoker presented in autumn 2010 with a 4-month history of a left-sided neck mass and a 6-month history of odynophagia. Nasendoscopy confirmed supraglottic viable tumour, which subsequent biopsy confirmed as a poorly differentiated SCC.

CT revealed a supraglottic mass centred on epiglottis extending to the left pyriform fossa, magnetic resonance imaging (MRI) confirmed this to be T4 N2b SCC of the supraglottis. Surgery was not deemed appropriate due to the neck mass encasing the carotid vessels, see Figure 2a.

She underwent three cycles of induction chemotherapy with cisplatin 75 mg/m^2 and 5FU 3000 mg/m^2 from 21st October 2010–3rd December 2010 with little response, see Figure 2b. She subsequently received radical radiotherapy 70 Gy in 35 fractions from 10th January 2011–25th February 2011 with weekly cetuximab and clinically had a complete response. An end of treatment positron emission tomography scan did show some residual activity at 3 months, however, biopsy confirmed this to be benign reactive change.

She remains alive and well at the time of submission. The above cases represent ~1% of cases treated in the department per year.

DISCUSSION

The above cases challenge the traditional belief that response to chemotherapy can reliably predict one's response to radiotherapy. Patients who have a poor response to induction chemotherapy are less likely to respond to radiotherapy, probably due to the inherent biology of the tumour. However, a good response to induction chemotherapy does not guarantee response to radiation and should not be used as the only principle for planning future treatment.

Current clinical trials utilising induction chemotherapy generally use response as a selection criteria for proceeding to radiotherapy. In this setting, lack of response to chemotherapy could therefore condemn a patient to a laryngectomy, which can have a negative impact on quality of life.[2]

Concurrent cetuximab radiotherapy was chosen in the above cases as a radical treatment option as an alternative to palliative radiotherapy for a number of reasons; first cetuximab is known to act as a potent radiosentisiser as demonstrated by Bonner et al., second there is phase II and phase III trial data to suggest that cetuximab is effective in recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) that has progressed or is

https://doi.org/10.1017/S1460396912000532 Published online by Cambridge University Press

resistant to platinum-based chemotherapy.[6,8–11] It is however also possible that response may be independent of EGFR inhibition and attributable to radiotherapy alone.

Cetuximab is the first targeted therapy to confer a survival benefit in SCCHN. Bonner et al.[12] demonstrated significantly improved locoregional control and 5-year overall survival (OS) (45·6% versus 36·4%) when radiation plus concurrent cetuximab was compared with radiation alone.

Concomitant cisplatin is associated with a consistent 6·5% OS benefit at 5 years.[13] Cetuximab and cisplatin have complementary mechanisms of action; cetuximab preventing signal transduction to the nucleus and cisplatin preventing cell division by cross linkage of DNA, therefore any multiplication signal that may pass to the nucleus should not instruct the cell to divide. The main side effects of cetuximab include acneiform rash, diarrhoea and hypomagnesaemia compared with ototoxicity, nephrotoxicity, emesis and neurotoxicity with cisplatin. Given their non-overlapping toxicity profiles and potential synergism with radiation there has been considerable interest in combining the two agents, both sequentially and concurrently.

Recent trials have investigated the role of cetuximab in the radical treatment of SCCHN further. The RTOG 0522 trial presented at ASCO 2011 compared concurrent accelerated radiation plus cisplatin with or without cetuximab for 940 patients with stage III–IV oropharynx, larynx, and hypopharynx SCC.[14] No significant differences were found in either progression free survival (PFS) (2 year: 63% versus 64%, HR 1·05, 0·84–1·29; $p = 0·66$) or OS (2 year: 83% versus 80%, HR 0·87, 0·66–1·15; $p = 0·17$).

TREMPLIN, a phase 2 trial comparing concomitant cisplatin radiotherapy with cetuximab radiotherapy following response to three cycles of induction TPF chemotherapy demonstrated a similar local failure rate of 10% versus 8·9%, but a higher number of patients within the cetuximab arm (71% versus 43%) received all intended cycles.[15]

Rampino et al.[16] recently reported results from a phase 2 trial where two cycles of TPF induction chemotherapy was followed by radiotherapy plus weekly cetuximab for 36 patients with stages 3 and 4 SCC of the oral cavity, oropharynx, larynx or hypopharynx. Overall response rates of 81·8% with 60·6% achieving a complete response were reported. This trial did not use the traditional 'chemoselection' design and outcomes of similar trials investigating this area further are awaited with interest.

The above cases add support for cetuximab radiotherapy following failure of TPF induction chemotherapy in appropriate patients. The role of monoclonal antibodies demands further research, particularly in the context of presumed chemotherapy resistance.

Acknowledgement

The authors thank Mr Mark Lewis for image support.

Conflict of interest

None.

References

1. The Department of Veterans Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. N Engl J Med 1991; 324: 1685–1690.
2. Hanna E, Sherman A, Cash D et al. Quality of life for patients following total laryngectomy vs. chemoradiation for laryngeal preservation. Arch Otolaryngol Head Neck Surg 2004; 130: 875–879.
3. Forastiere A A, Goepfert H, Maor M et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med 2003; 349: 2091–2098.
4. Pointreau Y, Garaud P, Chapet S et al. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. J Natl Cancer Inst 2009; 101 (7): 498–506.
5. Zhang N, Erjala K, Kulmala J et al. Concurrent cetuximab, cisplatin, and radiation for squamous cell carcinoma of the head and neck in vitro. Radiother Oncol 2009; 92 (3): 388–392.
6. Bonner J A, Harari P M, Giralt J et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 2006; 354: 567–578.
7. Burtness B, Goldwasser M A, Flood W et al. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and

neck cancer: an Eastern Cooperative Oncology Group Study. J Clin Oncol 2005; 23: 8646–8654; Erratum, J Clin Oncol 2006; 24: 724.

8. Vermorken J B, Trigo J, Hitt R et al. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. J Clin Oncol 2007; 25: 2171–2177.
9. Baselga J, Trigo J M, Bourhis J et al. Phase II multicenter study of the antiepidermal growth factor receptor monoclonal antibody cetuximab in combination with platinum-based chemotherapy in patients with platinum-refractory metastatic and/or recurrent squamous cell carcinoma of the head and neck. J Clin Oncol 2005; 23: 5568–5577.
10. Herbst R S, Arquette M, Shin D M et al. Phase II multicenter study of the epidermal growth factor receptor antibody cetuximab and cisplatin for recurrent and refractory squamous cell carcinoma of the head and neck. J Clin Oncol 2005; 23: 5578–5587.
11. Vermorken J B, Mesia R, Rivera F et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 2008; 359: 1116–1127.
12. Bonner J A, Harari P M, Giralt J et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. Lancet Oncol 2010; 11 (1): 21–28.
13. Pignon J P, le Maître A, Maillard E et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. Radiother Oncol 2009; 92: 4–14.
14. Ang K K, Zhang Q E, Rosenthal D I et al. A randomized phase III trial (RTOG 0522) of concurrent accelerated radiation plus cisplatin with or without cetuximab for stage III–IV head and neck squamous cell carcinomas. J Clin Oncol 2011; 29 (suppl., abstract 5500)
15. Lefebvre J, Pointreau Y, Rolland F et al. Sequential chemoradiotherapy (SCRT) for larynx preservation (LP): results of the randomized phase II TREMPLIN study. J Clin Oncol 2011; 29 (suppl., abstract 5501)
16. Rampino M, Bacigalupo A, Russi E et al. Efficacy and feasibility of induction chemotherapy and radiotherapy plus cetuximab in head and neck cancer. Anticancer Res 2012; 32 (1): 195–200.

https://doi.org/10.1017/S1460396912000532 Published online by Cambridge University Press