Received:
29 January 2016

Revised:
26 September 2016

Accepted:
11 October 2016

<https://doi.org/10.1259/bjr.20160105>

Cite this article as:

Caroline B, Sundus Y, Dawn D, Carol G, Susan M. Cost analysis of cetuximab (Erbix) plus radiotherapy (ERT) versus concomitant cisplatin plus radiotherapy (CRT) within an NHS oncology unit (single institution): a pilot study. *Br J Radiol* 2016; **89**: 20160105.

FULL PAPER

Cost analysis of cetuximab (Erbix) plus radiotherapy (ERT) versus concomitant cisplatin plus radiotherapy (CRT) within an NHS oncology unit (single institution): a pilot study

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Objective: The aim of this feasibility study is to define the resource effectiveness of cetuximab vs cisplatin given concomitantly with radiotherapy for squamous cell carcinoma within a National Health Service clinical oncology unit.

Methods: 20 patients with Stage 3 or 4 head and neck squamous cell cancers were randomized to receive either cetuximab with radiotherapy (ERT) or cisplatin with radiotherapy concurrent with external beam radiotherapy 70 Gy in 35 fractions on a 1:1 basis over a 12-month duration. The study compared the resource utilization of ERT vs cisplatin with radiotherapy taking into account drug costs, clinical management and the costs of managing treatment-related toxicity from first fraction of radiotherapy to 6 months after the completion of therapy. Outcome measures were quality of life (recorded at the entry, end of radiotherapy, 6 weeks post treatment and 6 months post treatment), admissions to hospital, delays to radiotherapy, locoregional control and survival.

Results: Total drug costs including cost of nutritional supplements for patients treated with cetuximab were £7407.45 compared with £3959.07 for patients treated with cisplatin. Unscheduled admissions for toxicity management were significantly more common in the ERT arm. Healthcare personnel spent significantly more time delivering unscheduled outpatient care for patients receiving cisplatin than for those receiving cetuximab

($p = 0.01$). No significant difference in the quality of life was suggested at baseline, 6 weeks and 6 months. The mean time to removal of percutaneous gastrostomy (PEG) after completion of radiotherapy was 49.7 weeks in the cisplatin arm and 18.5 weeks in the cetuximab arm ($p = 0.04$). There was a statistically significant difference in patient-reported use of PEG between the cisplatin and cetuximab arms at 6 months following completion of treatment ($p = 0.04$). At 21 months, overall survival was 80% in the cisplatin arm vs 50% in the cetuximab ($p = 0.332$), with disease-free survival being 80% in the cisplatin arm vs 40% in the cetuximab ($p = 0.097$).

Conclusion: Cetuximab is still more expensive in simple drug cost terms than cisplatin when delivered with radiotherapy taking into account costs of drugs for toxicity management and nutritional supplements but other resource implications such as inpatient admission, time spent delivering unscheduled care and cost of additional investigations to manage toxicity for patients treated with cisplatin significantly reduce differential. The study suggested significant differences in patient-reported PEG use at 6 months and in time to PEG removal in favour of the cetuximab arm.

Advances in knowledge: There is paucity of randomized data on cost analysis for cisplatin vs cetuximab radiotherapy; this trial informs on the cost analysis between the two approaches.

INTRODUCTION

Concomitant cisplatin and radiotherapy is an established treatment for Stages 3 and 4 squamous cell carcinoma of the head and neck. Bonner et al^{1,2} suggested that addition of cetuximab to radiotherapy improved local control and overall survival (OS) in patients with locally advanced

carcinoma of the head and neck. This led to cetuximab and radiotherapy being approved by the UK National Institution for Health and Care Excellence as an option for radical potentially curable therapy for patients who are unable to receive radiotherapy plus concomitant platinum therapy in the UK.³

Although the drug cost for cetuximab (approximately £5000 total for cetuximab alone) when used concomitantly with radiotherapy [cetuximab with radiotherapy (ERT)] is higher than the drug cost of cisplatin (approximately £500 in total for cisplatin including antiemetic) when used concomitantly with radiotherapy [cisplatin with radiotherapy (CRT)], it was hypothesized that some or all of the additional costs of ERT could be offset against the cost of managing acute toxicity. Data quantifying the impact on available resources is essential for the managed entry of new drugs into clinical practice for National Health Service (NHS) Trusts and Cancer Networks in the UK.

A randomized study was designed to compare resource implications in both arms of the study. This was deemed pertinent, as otherwise a retrospective audit to investigate this issue in the UK would have been subject to the confounding factor of comorbidity, as patients treated with ERT in the UK must have comorbidity which precludes platinum therapy (cisplatin or carboplatin); hence, high risk of introduction of bias to the result of any cost analysis.

The study was designed as a pilot study to investigate whether a larger study comparing the quality of life in patients treated with CRT vs ERT was feasible (EU Clinical Trials Register EUCTR2007-002169-11-GB; for details, see Appendix A).

METHODS AND MATERIALS

20 (10 per study arm) patients with Stage 3 or 4 squamous cell carcinoma of the head and neck (oral cavity, oropharynx, larynx or hypopharynx) who were eligible for radical cisplatin-based chemoradiation were offered study participation. Those who consented to participate were prospectively randomized to receive either cisplatin or cetuximab with a standard course of radiotherapy (70 Gy in 35 fractions), following local protocols regarding percutaneous gastrostomy (PEG) insertion and monitoring during and after radiotherapy at New Cross Hospital, Royal Wolverhampton Hospitals Trust, Wolverhampton, UK. Patients were randomized to receive either cetuximab (loading dose 400 mg m^{-2} followed by weekly 250 mg m^{-2} with radiotherapy) or cisplatin 40 mg m^{-2} weekly $\times 6$ with radiotherapy concurrent with external beam radiotherapy 70 Gy in 35 fractions.

The study was designed to explore the differences in resources required to manage different toxicity profiles for ERT and CRT during the treatment, acute and late phase of treatment following standard local management protocols. For the purpose of this study, acute phase was defined as first to last fraction plus the first 6 weeks post radiotherapy, including the first dose of cetuximab and the late phase defined as 6 weeks to 6 months post treatment.

PEG insertion prior to the commencement of radiotherapy was dictated by local protocol and included all patients undergoing platinum-based chemotherapy; all patients undergoing radical irradiation of the oral cavity or a large volume of oropharyngeal mucosa (in the opinion of the treating physician); and patients who had pre-treatment dysphagia resulting in weight loss.

Owing to resource implications and difficulty in managing the acute admissions for nasogastric tube feeding and training during treatment, almost all patients were offered PEG insertion as outpatient procedure at this hospital.

Standard monitoring for all patients in the study included review prior to each administration of systemic anticancer therapy by the nursing team in the chemotherapy suite; weekly review by clinician; weekly on-treatment review by the specialist head and neck radiographer with referral to the dietician as required; and weekly review for 3 weeks after the last fraction in the multidisciplinary post-treatment toxicity clinic [led by the head and neck clinical nurse specialist (CNS), speech and language therapist (SALT) and a dietician]. The end of the acute phase corresponded to the routine scheduled review at 6 weeks following the completion of radiotherapy. Monthly review in the late phase corresponded to standard monthly follow-up in the first year after radical treatment. During this period, all interactions with the healthcare professionals were recorded prospectively. Interactions with the healthcare professionals who were not core members of the head and neck multidisciplinary team were classified as non-routine care and those with the head and neck team as routine care. Contacts between study participants and members of the head and neck team were prospectively timed while the following estimations of the time spent with the patient was applied to contacts with non-head and neck team health care professionals to all health care professional/patient interactions in both arms of the study. This was an average time deemed reasonable by the head and neck team for assessment since non-routine interactions were unplanned and hence the length of time could not be recorded, requiring the best possible estimation of the length of time for each assessment:

- full history = 10 min
- full examination = 10 min
- specific individual symptom review = 10 min
- requesting a test and follow-up of result = 10 min (5 min to request and/or 5 min to review the result)
- telephone call for advice = 5 min
- writing a prescription = 5 min.

Details of all drugs and dietary supplements prescribed, all radiology and laboratory test requested, all unplanned admissions, and all radiotherapy and chemotherapy delays in treatment were collected for both the acute and late phases. Radiology investigations requested for the sole purpose of directing management of primary cancer (*i.e.* positron emission tomography scans) were not included in the analysis except for those performed to aid management suspected of treatment-related side effects. Secondary outcome measures included local control, OS and quality of life.

The quality of life questionnaires EORTC QLQ 30 and QLQ-H&N35 were completed by the patient at study entry, on the last day of radiotherapy, at 6 weeks following completion of radiotherapy and at 24 weeks following completion of radiotherapy.

Prior to commencing the study, a time and motion study was carried out to investigate the amount of time spent in pharmacy for dispensing and preparing both treatment regimens and the direct nursing time required in the chemotherapy suite for each regime, if no complications or additional interventions were given to the patient over and above simple delivery of the treatment. This indicated that mean chemotherapy nursing time required for delivery of cisplatin was 133 min/patient/cycle and for cetuximab 68 min/patient/cycle.

Pharmacy preparation time for both drugs was equivalent. Nursing staff and paramedical personnel recorded the duration and nature of any additional intervention or direct contact over and above simple delivery of the treatment schedule.

OS in the study is defined as the period of time from the last day of treatment until death and progression-free survival (PFS) as the period of time from the last day of treatment to the first detection of recurrence.

Inclusion criteria

All patients eligible to enter the trial were offered participation in the study to avoid selection bias. Patients with TNM Stage 3 or 4 (7th edn), squamous cell carcinoma of the oropharynx, larynx and hypopharynx suitable for radical primary treatment with cisplatin-based chemoradiotherapy 70 Gy in 35 fractions in the opinion of treating clinical oncologist were eligible for randomization into the study.⁴

Required haematological parameters at study entry were absolute neutrophil count $>1.5 \times 10^9 \text{ l}^{-1}$, platelet count $>100 \times 10^9 \text{ l}^{-1}$, haemoglobin level $>100 \text{ g l}^{-1}$, Cockcroft Gault-calculated Glomerular Filtration rate of $>60 \text{ ml min}^{-1}$, bilirubin level within normal limits and alanine transferase $<1.5 \times$ upper limit of normal with alkaline phosphatase $<2.5 \times$ upper limit of normal. Patient compliance and geographic proximity allowing for adequate follow-up were taken into consideration.

Exclusion criteria

Patients who received neoadjuvant chemotherapy, prior surgery for the primary site (neck dissection was allowed), any investigational drug within 4 weeks of study entry, uncontrolled infection, pre-existing peripheral neuropathy or distant metastases were excluded from entering the study.

Concomitant cisplatin chemoradiotherapy schedule
Cisplatin 40 mg m^{-2} was administered weekly over 2 h with 1 l of normal saline pre- and post-hydration (over 2 h) (as per standard local protocol) delivered concomitantly with 70 Gy in 35 fractions of radiotherapy daily for over 47 days. Antiemetics for the trial protocol included 8 mg of Ondansetron intravenously and 8 mg of dexamethasone intravenously given concomitantly with chemotherapy and post-chemotherapy oral Ondansetron 8 mg twice a day for 3 days. As discussed earlier, all patients underwent prophylactic PEG placement prior to commencing radiotherapy as departmental protocol.

Once treatment was completed, patients were evaluated by the dietician and SALT for oral intake. If this was 100% and weight maintained over a month, the PEG tube was removed.

Concomitant cetuximab and radiotherapy schedule
Cetuximab 400 mg m^{-2} (over 2 h) commencing 1 week prior to radiotherapy followed by cetuximab 250 mg m^{-2} (over 1 h) weekly during radiotherapy 70 Gy in 35 fractions of daily radiotherapy over 47 days. PEG insertion protocol followed as discussed above.

Analysis

The acute phase-monitoring period ran from the first fraction of radiotherapy (inclusive of the first dose of cetuximab) to 6 weeks

following the last fraction of radiotherapy. The treatment phase was determined as the time between the first and the last fraction of radiotherapy and was included within the acute phase. The late phase-monitoring period ran from the end of the acute phase to 24 weeks following completion of radiotherapy. All patients were included in analysis of the treatment phase. Patients whose tumour recurred or who died during one of the assessment phases were withdrawn from the study and therefore excluded from analysis of that and subsequent phases. This was to ensure treatment cost associated with recurrence or second primaries would not be relevant to the toxicity of treatment under investigation.

Cost was calculated for all phases in terms of overall financial cost of drugs prescribed (excluding routine concomitant medication for comorbid conditions prescribed prior to study entry), investigations requested and food supplements required. A further analysis estimated total nursing, radiographer, medical personnel (with the exception of the patient's general practitioner), SALT and dietician time spent with each patient.

All hospital visits/interventions during the acute phase were included in the analysis. In the late phase, only hospital admissions/visits/interventions thought to be directly related to the patients' head and neck cancer treatment by the chief investigator were included in the analysis.

If the patient's cancer recurred within an assessment phase, costs associated with tumour recurrence in the opinion of the principal investigator were not included in the analysis.

Data were retrieved from data collection forms and review of the medical notes.

Follow-up schedule

Patients were reviewed weekly during radiotherapy and weekly following radiotherapy until discharged from the post treatment toxicity clinic by the CNS as local protocol (weekly for minimum of 3 weeks until the radiotherapy reaction had peaked and begun to settle). Patients were then reviewed at the end of the acute phase at 6 weeks following completion of radiotherapy and thereafter monthly for a period of 5 months.

Randomization

Patients were randomized on a 1:1 basis to the study over a 24-month duration. 20 sealed envelopes were held by the research and development department at the study institution (New Cross Hospital, Wolverhampton), each containing a card with either cisplatin or Erbitux® (Merck KGaA 64271, Darmstadt, Germany) written on it. An envelope was selected by an individual independent from the study for each individual patient. No balancing of study groups was attempted at randomization.

Statistical analysis

The study was designed as a pilot study intended for exploratory analysis, hence no attempt was made for a power calculation.

Since the number of patients in the study was small, a two-tailed paired *t*-test was used to assess differences between study groups

for mean time to percutaneous gastrostomy tube removal and differences in estimated total time for unscheduled care.

The log rank (Mantel–Cox) test, using Graphpad Prism software (La Jolla, CA), was used to assess OS and local recurrence-free survival. OS was defined as the time from last radiotherapy fraction to death or the censor date, and local recurrence-free survival was defined as the time from last radiotherapy fraction to first detection of local recurrence or the censor date.

Differences between the two groups for patient-reported use of percutaneous gastrostomy tube and number of admissions during the acute phase were assessed using the χ^2 test for statistical significance.

An unpaired two-tailed *t*-test was used to evaluate differences between European Organisation for Research and Treatment of Cancer quality of life questionnaire parameter scores.

Drug and nutritional supplementation costs were expressed as mean cost per patient in each arm.

The statistical calculations of *t*-test and χ^2 test were carried out using Microsoft® Excel® (Microsoft, Redmond, WA) software.

RESULTS

Patient characteristics and treatment delivered

Table 1 shows patient characteristics in both arms of the study. Randomization resulted in study groups being equally matched for age, sex, tumour stage and primary site.

All patients were of performance status 0 or 1 at the time of study entry. 16 patients, 8 in each arm, had primary tumours of the oropharynx, and the remainder being laryngeal or hypopharyngeal primaries. Patient characteristics in both arms of the study were equally matched for age, sex and stage.

Drug dose intensity was 90% in the cisplatin arm and 88.75% in the cetuximab arm. 100% of patients in the cetuximab group received the prescribed dose of 70 Gy compared with 95% of patients in the cisplatin group; one patient received 66 Gy as treatment was curtailed due to acute toxicity. Two patients in the cetuximab group had unplanned uncompensated breaks in treatment of 24 h. Five patients in the cisplatin arm, including the patient whose treatment was curtailed early, had unplanned breaks in treatment; with the exception of the patient whose treatment was completed early due to acute toxicity, all breaks during CRT were compensated in accordance with the Royal College of Radiologists guidelines.⁵

All patients in the study were included in the analysis of the treatment phase. Two patients were withdrawn from the analysis of the acute phase, one in each arm of the study, as one patient died due to pneumonia in the acute phase and another was found to have a synchronous primary requiring additional treatment. One patient in the cisplatin arm of the study was found to have developed metastatic disease in the late phase of the study and therefore was withdrawn at completion of the acute phase for the analysis (Figure 1).

At the censor date of 31 October 2013, five patients had developed second primaries and all had died as a result of the second

Table 1. Patient and treatment characteristics

Characteristics	Cetuximab <i>n</i> = 10		Cisplatin <i>n</i> = 10	
Sex	3 females	7 males	3 females	7 males
Age (in years)	Median = 60		Median = 59.5	
	44–66		45–74	
Site	Oropharynx = 8		Oropharynx = 8	
	Larynx/hypopharynx = 2		Larynx/hypopharynx = 2	
Stage	Stage 3 = 3		Stage 3 = 3	
	Stage 4a = 2		Stage 4a = 1	
	Stage 4b = 5		Stage 4b = 6	
Unplanned breaks in radiotherapy delivery	2 One patient too ill to attend on 1 day One patient delayed by 1 day, as second mould required due to weight loss Both episodes uncompensated		5 Three patients too ill to attend One patient delayed due to PEG fitting during treatment (patient refused PEG pre treatment) All above compensated by bd fractions One treatment stopped early due to toxicity at 66 Gy	
Concomitant drug dose intensity delivered	88.75%		90%	
Radiotherapy dose delivered	100% of patients received prescribed dose of 70 Gy		95% of patients received prescribed dose of 70 Gy	
			5% (one patient) received 66 Gy. Treatment curtailed due to acute toxicity	

PEG, percutaneous gastrostomy.

Bd; Twice a day.

primary diagnosis: one patient in the cetuximab arm of the study (primary carcinoma of the bronchus) and four in the cisplatin arm (three bronchial carcinoma and one oesophageal carcinoma).

There was no difference in OS between the two arms of the study [$p = 0.83$, log rank (Mantel-Cox) test] as shown in Figure 2. However, as this was a pilot study, the study was not powered to detect any differences in survival.

Although local recurrence was not an objective for the study, a statistically significant difference in local recurrence was detected between the two arms. Local recurrence-free survival being 100% in the cisplatin arm and 50% in the cetuximab arm [$p = 0.022$, log rank (Mantel-Cox) test].

9 out of 10 patients in the cisplatin arm of the study required unplanned supportive treatment during an unplanned admission, either day case or overnight stay. For those in the cetuximab arm, 2 out of 10 patients required admission. This was a statistically significant difference, χ^2 ($p = 0.002$).

This corresponded to 9 overnight admissions (in total, across all follow-up phases) amounting to 60 nights, plus 4 additional day case treatment in total for the cisplatin group; and 4 overnight admissions (in total), amounting to 46 nights plus 1 additional day-case treatment for the cetuximab group. To estimate and compare cost per patient, overnight and day case admissions in the treatment and acute phase were costed using the Health Resource Group (HRG v. 4) codes for complex/major head and neck disorder applicable. Eight overnight admissions and 4 day cases for nine patients completing the acute phase of treatment

Figure 1. Total numbers of patients included in the analysis of each treatment phase.

Figure 2. Overall survival between the two arms of the study [$p = 0.83$, log rank (Mantel-Cox) test] as shown.

in the cisplatin arm and three overnight admissions and 1 day case for the nine patients completing the acute phase in the cetuximab arm were reviewed. This equated to an estimated cost of £2728 per patient for unplanned admissions in the cisplatin arm and £1187 per patient in the cetuximab arm.

Calculating the simple drug cost of the chemotherapy including the cost of antiemetics and pre hydration and post hydration, the mean cost of treatment in the study was in total £361.41/patient in the cisplatin group and £5142.95/patient in the cetuximab group. For supportive medications not routinely prescribed on the chemotherapy template, the mean costs in the acute phase (includes treatment phase) using the British National Formulary list price were £720.89/patient for patients treatment with cisplatin and £608.90/patient for those treated with cetuximab. For the late phase, costs were £248.65/patient vs £172/patient for cisplatin and cetuximab, respectively. In total, for all phases, the mean cost of supportive drugs for the duration of the study was £969.54/patient in the cisplatin arm and £720.90/patient in the cetuximab arm; whereas, the total cost of systemic anticancer therapy prescriptions and supportive drugs was £1331.01/patient for cisplatin and £5923.85/patient for cetuximab.

All patients in the CRT arm of the study underwent PEG placement, and 9 out of 10 patients underwent PEG placement in the ERT arm of the study. There was a significant difference in patient-reported use of percutaneous endoscopic gastrostomy tube between the cisplatin and cetuximab arms at 6 months (χ^2 ; $p = 0.04$), five out of eight patients treated with cisplatin were still using the PEG tube, although not necessarily for all intake, at 6 months, compared with one out of eight in the cetuximab-treated arm. A lower degree of PEG dependency for the cetuximab arm was also shown by a reduction in mean time to removal of the PEG. The mean time to PEG removal from the last radiotherapy fraction in the cetuximab-treated group being 18.5 weeks compared with 49.7 weeks in the cisplatin arm (t -test; $p = 0.04$).

Dietary supplements prescribed cost £1115.62/patient (during treatment/acute phase) and £1512.5/patient (in the late phase), respectively, for patients treated with CRT compared with £909.60/patient (in treatment/acute phase) and £634/patient (in late phase), respectively, for those undergoing ERT. This equated to a mean total cost per patient for the duration of the study of £2628.12/patient for cisplatin-based treatment and £1543.60 for cetuximab-based treatment.

Total estimated non-routine care during the acute phase for non-head and neck team personnel seemed to be significantly greater in the cisplatin-treated group where patients had an estimated 107 min/patient unscheduled contact with healthcare professionals compared with 48 min/patient in the cetuximab arm (t -test $p = 0.01$). The estimated additional time and number of contacts with each professional group are shown for health-care professionals in Table 2.

In total, drug costs including supportive medications, systemic anticancer drugs and cost of nutritional supplements per patient treated with cetuximab were £7407.45 compared with £3959.07 per patient treated with cisplatin.

There was no significant difference in time spent in care in outpatients between the two arms of the study for dietician, SALT or head and neck CNS input for the acute phase. There was a suggestion of reduced input required by the dietician, SALT or head and neck CNS in the late phase for patients in the cetuximab arm of the study, but this failed to reach significance, t -test $p = 0.29, 0.30$ and 0.27 , respectively (Table 3).

Patients receiving cisplatin and radiotherapy required twice the number of radiology and laboratory investigations, during the acute and treatment phases, than those who received treatment with cetuximab and radiotherapy. For radiology, this equated to 1.5 investigations/patient treated with cisplatin and 0.7 investigations/patient for those treated with cetuximab. For laboratory investigations, this equated to 44.3 investigations/patient treated with cisplatin vs 18.3 investigations/patient for those treated with cetuximab. For cetuximab patients, all laboratory tests during the treatment and acute phase were performed for the purposes of toxicity management, whereas in the cisplatin arm, 54.6% of all investigations in this phase were performed for toxicity management and the remainder as routine management for chemotherapy delivery.

In the late phase, numbers of investigations requested for management of toxicity were small in both arms but were more frequently required in the cetuximab arm of the study.

1 radiographic and 7 blood tests were requested for the 8 patients entering the late phase in the cisplatin-treated group vs 3 radiographic and 34 blood tests for the 9 patients entering the late phase in the cetuximab-treated group.

There was no suggestion of differences in quality of life scores for function, symptoms or global quality of life at baseline, end of treatment, 6 weeks or 6 months after radiotherapy completion.

DISCUSSION

The primary aim of the study was to attempt to evaluate the difference in overall cost (monetary terms) between the two arms of the study, taking into consideration the management of side effects in the first 6 months after treatment. This was to fully take into account the cost for a larger study which may evaluate 12 differences in the quality of life between patients treated with cisplatin or cetuximab given concomitantly with radiotherapy for squamous cell carcinoma of the head and neck. The internal market within the UK NHS made this aim difficult to achieve, as cost in pure terms is not a constant and is dependant on where the cost is applied, *i.e.* primary care trust or the acute hospital. The study has therefore evaluated the use of resources wider than the cost in financial terms, *i.e.* investment in time for staff, use of drugs and investigations which were simpler to identify unequivocally. The costs associated with the management or investigation of recurrence have not been taken into account. This was due to the study being underpowered to detect any differences in recurrence between the two arms. Since any differences in recurrence occurring by chance could have significant impact the costs of treatment, it has been assumed for the study that these costs would be the same.

Cetuximab given concomitantly with radiotherapy has been shown to significantly improve OS for patients with locally advanced squamous cell carcinoma of the head and neck, with data showing a 57% OS at 3 years compared with 44% in patients treated with radiotherapy alone, $p = 0.02$.^{1,2,6} Several trials have previously reported on the efficacy of chemotherapy concurrent with radiotherapy, and this is considered to be the standard of

Table 2. Additional outpatient non-routine/one emergency care provided in the acute phase (excludes specialist head and neck team contacts)

Type of review	Cisplatin arm 10 patients		Cetuximab arm 10 patients	
	Total number of non-routine care (min)	Number of additional contacts	Total number of non-routine care (min)	Number of additional contacts
Junior medical doctor	600	20	215	9
Registrar (senior doctor)	65	6	130	8
Therapy radiographer	65	11	20	4
Nursing staff	340	17	115	7
Total	1070	54	480	28

Table 3. Total outpatient care provided by head and neck team

Type of review	Acute phase additional time in minutes/patient		Late phase additional time in minutes	
	Cisplatin	Cetuximab	Cisplatin	Cetuximab
Dietician	96.1 min	93.5 min/	46.5	24
Head and neck CNS	114.2	97	44	28
Speech and language therapy	58.3	17	64.3	32.7

CNS, clinical nurse specialist.

care for patients with head and neck cancer, but there has been to date no randomized trials comparing cetuximab chemo-radiotherapy vs cisplatin chemoradiotherapy.⁷

Panitumumab, a fully humanized anti-epidermal growth factor receptor monoclonal antibody, in combination with radiotherapy has been evaluated in randomized trials compared with cisplatin plus radiotherapy, both alone and in combination.^{8,9} In these studies, panitumumab plus cisplatin was not found to be superior to cisplatin alone, but panitumumab alone in combination with radiotherapy was found to be inferior to cisplatin chemoradiotherapy. The PFS was statistically significant in the human papillomavirus (HPV)-negative tumour population.⁷ In our study, tumour biopsies have not been tested for HPV, but it is hypothesized that our group consists of mainly HPV-negative population due to their smoking history. This may explain the lower local control rates in the cetuximab arm in this study.

Current literature evaluating the cost effectiveness and direct comparison between the two drugs is extremely limited. Brown et al¹⁰ have reported on separate analyses for five European countries: Belgium, France, Italy, Switzerland and the UK.¹⁰ The study estimated the cost-effectiveness of cetuximab in combination with radiotherapy compared with radiotherapy alone for the treatment of locally advanced head and neck cancer in patients for whom chemoradiotherapy is inappropriate or intolerable. It was shown that quality-adjusted life years (QALY), PFS and OS were better in the cetuximab and radiotherapy arm vs radiotherapy alone. Although the total treatment costs are predictably greater in the cetuximab and radiotherapy arm, it was balanced by incremental costs per additional QALY. The total estimated UK cost, including cost for cetuximab, radiotherapy, administration, adverse events, imaging, monitoring and procedures, was €18,972, excluding additional palliative and salvage treatments; this equates to £12,730 (1€ = 0.671 GBP; November 2006), with cost per QALY gained in UK being £6135.

Health technology assessment by the UK National Institution for Health and Care Excellence gave similar results, judging cetuximab plus radiotherapy to be cost effective compared with treatment with radiotherapy alone for patients of good performance status with locally advanced squamous cell cancer of head and neck to be £6390 per additional QALY.¹¹

Our study revealed that a higher number of radiological investigations were required in the cisplatin cohort in the acute phase

although the numbers were small. A similar result was seen for laboratory investigations with significantly more investigations performed in the cisplatin arm in the acute phase. Most of the differential in laboratory investigations occurred as a result of the increased routine monitoring required for treatment with cisplatin compared with that for cetuximab.

Patients in the cisplatin arm of the study underwent weekly monitoring of blood counts, and renal and liver functions prior to weekly chemotherapy delivery. Laboratory investigations for toxicity management accounted for all of the laboratory investigations in the treatment and acute phase for the cetuximab arm but only 54.6% of the investigations in the treatment and acute phase in the cisplatin arm.

Cisplatin-based chemoradiotherapy for head and neck cancer is associated with increased mucositis and dysphagia when compared with treatment with radiotherapy alone.¹² Local practice was to insert a percutaneous endoscopic gastrostomy feeding tube (PEG) prior to the delivery of concomitant chemoradiotherapy. Our results showed significantly more prolonged PEG dependence in the cisplatin trial arm compared with the cetuximab cohort. Utilization of food supplements in the late phase was similarly increased in the cisplatin group with correspondingly higher cost. In this cohort, however, PEG dependence was significantly longer than has previously been noted in our unit by local audit. Koutcher et al¹³ in their retrospective review showed no statistically significant difference of feeding tube dependence when comparing cisplatin and radiotherapy vs cetuximab and radiotherapy. The Cleveland Clinic, OH, reports 77% of patients requiring PEG feeding at 3 months following cisplatin chemoradiation and 17% at 12 months requiring supplementary feeding (8% still PEG reliant). This was consistent with our local audit of PEG use following cisplatin-based chemoradiotherapy showing similar levels of PEG usage (13%) at 12 months.^{14,15}

Cisplatin-related adverse events often require considerable clinical follow-up (including hospitalization). Local audit showed a 19.6% incidence of mild to moderate renal dysfunction (grade 1–2) and 21.6% incidence of severe (grade 3–4) neutropaenia. This translated to an admission rate of 13.7% with neutropaenic fever.¹⁴ Other groups have reported similar toxicity outcomes. One similar study investigating chemoradiation for carcinoma of the larynx reported on 180 patients receiving concomitant cisplatin with radical radiotherapy. Of these, 47%

of patients were found to develop grade 3 or 4 neutropaenia and 4% developed severe (grade 3–4) renal toxicity.¹⁶ This is in keeping with our study results which revealed a higher rate of hospital inpatient admission receiving the cisplatin arm with the associated costs.

It was deemed necessary to analyse personnel cost by estimating the time spent with the patient in minutes and to subdivide analysis into the head and neck team (consisting of CNS, SALT and dietician and head and neck oncologist) and non-head and neck team, as it was very difficult to separate routine care provided by the head and neck team and any additional care to standard care. It was therefore determined that all contacts with the head and neck team would be regarded as standard care and all contacts with staff outside the head and neck team would be regarded as unscheduled care. No significant differences were found between the two groups for time spent with the head and neck team. This reflects the complexity of care and the multi-disciplinary approach for all patients receiving radiotherapy for head and neck cancer in our unit. All patients were reviewed each week by the head and neck specialist radiographers, with onward referral to the dieticians as required during treatment. Additionally, the study patients were also reviewed weekly by the consultant oncologists managing patient care. After completion of a course of radiotherapy, all patients were routinely reviewed in a multiprofessional (the CNS, SALT and dietician) toxicity management clinic weekly until the acute reaction begins to subside (usually for the first 3 weeks following completion of treatment).

Contacts for non-routine/unscheduled care were significantly greater for patients in the cisplatin arm of the study than in the cetuximab arm, with the collective number of minutes of care being nearly double in the group treated with cisplatin (*t*-test; *p* = 0.01).

There was no statistically significant difference in quality of life parameters, but the reported use of PEG at 6 months following completion of treatment was significantly lower in the cetuximab group.

Bonner et al have shown 57% OS at 3 years with cetuximab compared with 44% in patients treated with radiotherapy alone, *p* = 0.02.^{1,2} Meta-analysis has also indicated that chemoradiation with cisplatin appears to confer an OS advantage of around 11% when compared with radiotherapy alone, but this is associated with a significant added acute and late toxicity.¹⁷ Accelerated, hyperfractionated radiotherapy has been shown to improve

survival when compared with conventional radiotherapy of five fractions a week.¹⁸ This is not necessarily the case with cisplatin-based accelerated chemoradiation where late toxic effects, especially with regard to swallowing dysfunction, are common.^{3,19} This may further improve the therapeutic ratio but is a subject for further studies.

In our study, the OS and disease-free survival were statistically insignificant between the two arms of the study, but the study was small and not designed to investigate survival differences. Local recurrence-free survival was significantly higher in the cisplatin arm (100% vs 50%) as compared with the cetuximab arm in our study, but the very small numbers in our study mean that no firm conclusions can be drawn from this. Patients in the cisplatin arm in this study had a higher incidence of second malignancy and distant metastasis leading to death, which may account for this. Koutcher et al¹³ have reported 2-year failure-free survival and OS rates of 87.4% vs 44.5% (*p* < 0.0001) and 92.8% vs 66.6% (*p* = 0.0003), respectively, in favour of cisplatin plus radiotherapy when compared with cetuximab and radiotherapy; however, this was a retrospective study with patient selection bias. This retrospective study showed better survival for the cisplatin arm as compared with the cetuximab arm; however, there has been no randomized control trial with direct comparison. Our study was not powered to detect survival difference, and it is not possible to make strong conclusions owing to the small sample size in our trial.

CONCLUSION

Cetuximab is still more expensive in monetary terms to Primary Care Trusts, with total drug costs including cost of nutritional supplements for patients treated with cetuximab being £7407.45 compared with £3959.07 for patients treated with cisplatin. However, human resource implications are more economical for cetuximab delivery in UK hospitals, once drug costs are recharged back to the commissioners. Toxicity costs for cisplatin significantly reduces differential particularly when the estimated costs for unscheduled hospital admission are taken into account.

The study showed significant differences in patient-reported PEG use at 6 months and time to PEG removal, but PEG use at 12 months in this study was higher than expected in the cisplatin-treated arm.

Although it is a small study and not powered to detect differences in survival, local recurrence rate seemed to be higher in the cetuximab and radiotherapy arm than in the cisplatin and radiotherapy arm.

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APPENDIX A

SCIENTIFIC TITLE

Cost Analysis Of Cetuximab (Erbix) Plus Radiotherapy (ERT) *vs* Concomitant Cisplatin Plus Radiotherapy (CRT) Within An NHS Oncology Unit (New Cross Hospital Wolverhampton): A Pilot Study—Cetuximab and Radiotherapt Cost Analysis Study.

MAIN ID

EUCTR2007-002169-11-GB.

SECONDARY ID

2007-002-0302-ONC.

REGISTER

EU Clinical Trials Register.

DATE OF REGISTRATION

26 November 2007.

DATE OF FIRST ENROLMENT

10 July 2008.

LAST REFRESHED

19 March 2012.