Cost Analysis Of Cetuximab (Erbitux) Plus Radiotherapy (ERT) Versus Concomitant Cisplatin Plus Radiotherapy (CRT) Within An NHS Oncology Unit (New Cross Hospital Wolverhampton): A Pilot Study

End of Study report

Author - Dr Caroline Brammer - Chief Investigator

Indication studied

stage 3/4 squamous cell carcinoma of the head and neck who are eligible for radical cisplatin based chemoradiation

Study Description

20 (10 per study arm) patients with stage 3/4 squamous cell carcinoma of the head and neck who are eligible for radical cisplatin based chemoradiation were randomised to receive either cisplatin or Erbitux concomitantly during a standard course of radiotherapy (70GY in 35 fractions), following local protocols regarding PEG insertion and standard monitoring during radiotherapy at New Cross Hospital, Wolverhampton. The study groups were compared with regard total planned and unplanned consultation time with medical and paramedical personnel, total administered drug costs (excluding pre-diagnosis medications) during the study period, total treatment delivery time and inpatient admission time. Unplanned gaps in radiotherapy and chemotherapy were documented.

The aim of the study was to compare the direct costs of ERT versus CRT taking in to account drug costs, clinical management and the costs of managing treatment related toxicity.

Name of the sponsor

The Royal Wolverhampton Hospitals NHS Trust

REC reference: 07/H030/105
Protocol Number: 2006-002-0201-ONC
EudraCT number :2007-002169-11
Development phase of study :Phase 4

Study initiation date = 24/09/2008
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The Study was carried out following the principles of GCP.Monitored by Research and Development (RWHT)
Report Date:21/09/12

SYNOPSIS

20 (10 per study arm) patients with stage 3/4 squamous cell carcinoma of the head and neck who are eligible for radical cisplatin based chemoirradiation were randomised to receive either cisplatin or Erbitux concomitantly during a standard course of radiotherapy (70GY in 35 fractions), following local protocols regarding PEG insertion and standard monitoring during radiotherapy at New Cross Hospital, Wolverhampton. The study groups were compared with regard consultation time with medical and paramedical personnel, total administered drug costs (excluding pre-diagnosis medications) during the study period and number of unplanned inpatient admissions. Unplanned gaps in radiotherapy and chemotherapy dose intensity were also compared. Approximate total treatment delivery time for both arms of the study was obtained from a time and motion study performed by one of the junior doctors in the department , recording the time taken for treatment preparation and delivery for 3 patients with no complications treated with weekly cisplatin and 3 patients with no complications treated with weekly Erbitux and a mean for both treatments taken

Data regarding investigations undergone during the study period were be obtained from the hospital radiology and pathology electronic systems. The patient had a routine weekly consultation with medical staff (a routine part of management) when a full drug history for that week was recorded. Oncology notes and main hospital records were be reviewed.

Nursing staff, Medical staff and paramedical personnel were asked to record the duration and nature of any additional intervention or direct contact over and above simple delivery of the treatment schedule (i.e. advice given) on the form attached to the patient's treatment sheet (Chemotherapy prescription or Radiotherapy prescription)..

The protocol required patients to complete the EORTC QLQ 30 and QLQ- H+N35 at study entry, on the last day of radiotherapy +/- 24 hours, at 6 weeks following completion of radiotherapy +/- 14 days and at 24 weeks +/- 14 days following completion of radiotherapy.

20 patients were be randomized on a 1:1 basis after informed consent had been obtained.

Data was collected for 2 predetermined phases of follow up. The acute phase monitoring period ran from randomization to 6 weeks following the last fraction of radiotherapy. The late phase ran from the end of the acute phase until 24 weeks after the completion of radiotherapy. All patients are routinely reviewed monthly following radical radiotherapy. All hospital visits/interventions during the acute phase (start of therapy to 6 weeks following the completion of radiotherapy) 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 in the assessment phase the patient was withdrawn from the study and, costs associated with tumour recurrence were not included in the analysis.

All inpatient stays in the acute and late phase were documented in terms of overall time in days, tests requested and drugs, medicinal devices and food supplements prescribed.

The above was analyzed in terms of overall financial cost of drugs, and medicinal devices, investigations performed and food supplements prescribed. An additional analysis estimated total nursing time, speech and language therapist and Dietitian time spent with each patient. Costs for inpatient stays and outpatient treatment was estimated from the UK Department of Health Price Tariff.

Data was be retrieved from data collection forms and review of the medical, dietetic and speech and language therapy records.

Patients were eligible for inclusion if the following criteria were met:

a) Patients with Squamous Cell Carcinoma of the Oropharynx, Larynx and Hypopharynx suitable for radical primary treatment with chemoradiotherapy in the opinion of treating clinical oncologist

Radiotherapy Schedule prescibed to be 70Gy in 35 fractions 5 fraction per week

b) TNM Stage 3 or 4 (7^{th} editiion)

c) Patient considered sutable to recieve cisplatin therapy in the opinion of treating clinical oncologist

d) Age 18-70

e) Expected survival greater than 6 months·

f) Patient able to give informed consent

g) Haematological Parameters at study entry: -

·Haematological Parameters at study entry: -

· Blood cell counts:

Absolute neutrophils > 1.5 x 10^9/L

Platelets > 100 x10^9/L

Haemoglobin > 10 g/dl (may be correcetd by transfusion where appropriate)

· Renal function:

EDTA-based glomelular filtration rate of > 50 mL/min or a cockcroft gault calculated GFR of > 60 mL/min.

· Hepatic functions:

Serum bilirubin within normal limits.

or AST or ALT < 1.5 x ULN with alkaline phosphatase < 2.5 x ULN.

h) Female patients potentially able to child bear should use an approved contraceptive method (IUD, birth control pills or barrier device) during and for 3 months after the study. All male patients should take adequate contraceptive precautions during and up to 2 months after the study

Patients with the following criteria were excluded

a) Palliative Radiotherapy

b) Accelerated Radiotherapy

c) Prior Radical Surgery for Primary Squamous Cell Carcinoma of the Head and Neck (neck disection is allowed)

d) Treatment within the last 4 weeks with any investigational drug.

e) Presence of distant metastases.

f) Evidence of uncontrolled infection.

g) Mental condition rendering the subject unable to understand the nature, scope and possible consequences of the study.

h) Neoadjuvant chemotherapy for squamous cell carcinoma of the head and neck prior to study entry.

i) Preexisiting peripheral sensory neuropathy

All patients who completed radiotherapy were included in the analysis for the acute phase

The QoL parameters for functional scores, symptom scores, global quality of life and head and neck symptom scores for both groups were assessed in terms of mean, standard deviation and difference between the populations were assessed using the unpaired t test.

Results

Patients receiving Cisplatin required more intense management during the treatment and acute phase they were more likely to require overnight admission and required mare laboratory and radiological investigation compared to those treatment with Cetuximab. Patients treated with Cisplatin also had more unplanned visits to hospital for management of the side effects of treatment. There was no significant difference between the two arm of the study for time spent with the head and neck CNS, Dietician or speech and language therapist.

There were no difference in quality of life parameters between the 2 arms of the study although patients treatment with Cetuximab were significantly less likely to be using a feeding tube at 6 months.

While the study was not powered to investigate survival or local recurrence rates there was a statistically significant increase in local recurrence in patients treated by Cetuximab in this study

Conclusion

While the overall costs of drug treatment plus emergency admission are higher for Cetuximab when compared to Cisplatin terms patients undergoing Cisplatin and Radiotherapy require significantly more non routine intervention and care than patients receiving Cetuximab and Radiotherapy in this randomised study and this should be taken in to account when planned further trials. A study comparing Cisplatin and Cetuximab to investigate quality of life and late functional effects of treatment could be viable within the NHS. Any future study should also be powered to investigate potential differences in overall survival and local recurrence rates

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Abbreviations

PEG	percutaneous Gastrostomy tube
EBRT	Cetuximab(Erbitux) plus Radiotherapy
CRT	Cisplatin plus Radiotherapy
RT	Radiotherapy
EORTC	European Organisation for Research and Treatment of Cancer
QLQ	Quality of Life Questionnaire
FDA	(US) Food and Drugs Administration
NICE	National Institute of Clinical Excellence
TNM	Tumour , Nodes, Metastasis (staging system)
EDTA	ethylenediaminetetraacetic acid
AST	Aspartate Transaminase
ALT	Alanine Transaminase
ULN	Upper Limit of Normal
FBC	Full Blood Count
U+E	Urea and Electrolytes
LFT	Liver Function Tests
MSU	Mid Stream Urine Sample
m.c.s.	microscopy, culture, sensitivity
CNS	Clinical Nurse Specialist
SALT	Speech and Language Therapist
i.v.	Intravenous
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PR	Partial Response
R+D	Research and Development
REC	Regional Ethics Committee
RWHT	Royal Wolverhampton Hospitals Trust
SAE	Serious Adverse Event
BNF	British National Formulary
HRG	Healthcare Resource Group
CT	Computed Tomography

Investigators And Study Administrative Structure

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Chief Investigator Acknowledgement:

I have read this report and confirm to the best of my knowledge it accurately describes the conduct and results of the study

Ethics

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. Patients were consented prior to any study procedures being undertaken specifically for the study.
All study documents and amendments were reviewed and approved by an Ethics Committee.

The Trial was reviewed by the East of England Rec office 1 Local Research Ethics Committee. Victoria House, Capital Park, Fulbourn, Cambridge, CB21 5XB

Introduction

Cetuximab given concomitantly with radiotherapy has been shown to significantly improve overall survival for patients with locally advanced squamous cell carcinoma of the head and neck in a phase 3 randomized trial which showed a 57% overall survival at 3 years compared 44% in patients treated with radiotherapy alone, p=0.02. [1]. Cetuximab and radiotherapy is considered an option for radical potentially curable therapy for these patients [2] and has been approved by the F.D.A. in the U.S.A and by NICE in the UK for this indication.

Meta analysis indicated that chemo radiation with cisplatin appears to confer an overall survival advantage of around 11% when compared to radiotherapy alone but this is associated with a significant added acute and late toxicity. [3] While Cetuximab given in conjunction with radiotherapy increases acute skin toxicity when compared to radiotherapy alone, this is reported to be manageable and there is no reported increase in late toxicity or treatment related mortality.[1] However there is no direct randomized clinical trial comparing outcomes from cisplatin based chemoradiotherapy and Cetuximab given concomitantly with radiotherapy although indirect comparisons between randomized trials suggest there is a similar gain in overall survival from either approach when compared to radiotherapy alone

Cisplatin related adverse events often require considerable clinical follow-up (including hospitalization). Local audit has suggested a 19.6% incidence of mild to moderate renal dysfunction (grade 1 and 2) and 21.6% incidence of severe (grade 3-4) neutropenia with a 13.7% admission rate with neutropenic fever. [6] This is similar to toxicity rate reported in the literature. From a study investigating chemoradiation for carcinoma of the larynx where 180 patients received concomitant cisplatin with radical radiotherapy 47% of patients were found to develop grade 3 or 4 neutropenia and 4 % developed severe (grade 3-4) renal toxicity. [4]

While the direct drug cost for Cetuximab (approx £ 5000 total for Cetuximab alone) when used concomitantly with radiotherapy is higher than the drug cost of cisplatin (approx £500 in total for cisplatin plus antiemetics alone) used concomitantly with radiotherapy, it is possible that some or all of the additional costs of ERT are off-set when follow-up analysis of cisplatin adverse event costs have been considered. Costing data is essential for the managed entry of new drugs into clinical practice for NHS Trusts and Cancer Networks in the UK. Also the development of oncology unit/cancer network Local Delivery Plans require cost data to assess the impact of new interventions upon the overall capacity of the Unit to deliver services. This study aimed to assess this as Cetuximab therapy may release resources in terms of the indirect costs (i.e. extra clinic staff time to treat cisplatin related AE's) while potentially providing the same overall survival advantage. Both arms of the study will used similar radiotherapy fractionation schedules of 70Gy in 35 fractions, 5 fractions per week and followed the local guidelines for on treatment review, routine post treatment follow up and prophylactic placement of percutaneous gastrostomy (PEG) tube (indications for PEG insertion being cisplatin chemoradiation, irradiation of oral cavity, Large volume irradiation, pre treatment weight loss or dysphagia). The patients in the study were followed for 12 months and all drugs prescribed, unplanned investigations and unplanned interventions were reviewed. Indirect later costs due to the management of recurrence where not included as it was assumed for the purpose of the study that recurrence rates would be similar in both arms

Study objectives

Primary Objectives

To compare the treatment costs of Cetuximab plus RT (EBRT)versus Cisplatin plus radiotherapy (CRT) taking in to account drug costs, clinical management and the costs of managing treatment related toxicity.

The primary outcome measure of the study is mean overall cost (in pounds sterling) of total therapy from randomization to the end of the late phase of the study follow up in both arms of the study.

Secondary Objectives

To document unplanned gaps in both radiotherapy and chemotherapy treatment delivery in both treatment arms

To document inpatient hospital admission rates in both treatment arms

To assess impact of treatment of Quality of Life

To assess median overall cost (in pounds sterling) of total therapy from randomization to the end of the late phase of the study follow up in both arms of the study.

Study design

20 patients with stage 3 or 4a or b squamous cell carcinoma of the head and neck suitable for potentially curative treatment with radical radiotherapy 70 Gy in 35 fractions plus concomitant weekly cisplatin (40mg/m2) were randomised to receive either Arm A; radical radiotherapy 70 Gy in 35 fractions plus concomitant weekly cisplatin (40mg/m2) or Arm B; radical radiotherapy, 70 Gy in 35 fractions, plus concomitant weekly Cetuximab (Erbitux) 250mg/m2 weekly following a 400mg/m2 loading dose the week prior to radiotherapy commencing.
Patients suitable for the study were identified at the weekly multidisciplinary Head and Neck Cancer Team meeting.
Prior to the study commencing 20 unmarked randomisation envelopes were prepared.10 contained one sheet of paper with the word Cetuximab and 10 containing a sheet of paper with Cisplatin written upon it. The pile of envelopes was then shuffled. To randomise a patient in to the study, clinicians rang the Research and Development office at New Cross Hospital Wolverhampton where one of the envelopes was chosen at random and opened.
Patients on the study were reviewed weekly during radiotherapy and a full drug history was taken and all investigations the patient had under gone in the previous week was recorded. Following treatment all patients were reviewed weekly in the clinical nurse specialist symptom review clinic until acute toxicity was settling following standard departmental protocols, at 6 weeks following completion of radiotherapy in the joint ENT/Oncology clinic then at monthly intervals. At each visit a full drug history was taken and unplanned interventions recorded. Dietary supplement requirements were recorded as well as time spent with clinical members of the head and neck team (specialist nurses, dieticians and speech and language therapy)
Quality of life questionnaires (EORTC QLQ 3o plus H+N 35) were to be completed at study entry prior to randomisation, on the last day of radiotherapy +/- 24 hours, at 6 weeks following completion of radiotherapy +/- 14 days and at 24 weeks +/- 14 days following completion of radiotherapy. [5,6]
The Study period was divided in to 3 periods “On treatment”, which covered the period of time from first treatment to the last day of treatment , “The Acute Phase” covering the period of time from first treatment until 6 weeks after the last treatment and the “Late Phase” covering the period of time from the end of the acute phase until 6 months after the end of treatment.

To assess the time taken to prepare and deliver the Cisplatin and Cetuximab a time and motions study was carried out to investigate how much time is spent in pharmacy dispensing and preparing both treatment regimes and how much time is direct nursing time is required in the chemotherapy suite for each regime if no complications or additional interventions are given to the patient over and above simple delivery of the treatment. The time and motion study was carried out for 3 patients receiving Cisplatin and 3 patients receiving Cetuximab and a mean was calculated. This mean for patients receiving cisplatin was applied to patients in arm A and the mean for patients receiving Cetuximab applied to patients in arm B. It was assumed that the time taken to deliver radiotherapy was the same in both arms.

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 (i.e. advise given) on the form attached to the patient's treatment sheet (Chemotherapy prescription or Radiotherapy prescription).

The Clinical Nurse Specialists, Dieticians and Speech and Language Therapist involved in study patients care recorded all contacts and interventions with the patient during the acute and late phases of study.

All investigations performed during treatment were documented and compared.
In the acute phase all investigations related to treatment and toxicity management were costed and analysed. In the Late phase only investigations relating to toxicity management were analysed for the purposes of the study. Investigations relating to confirmation of remission status or management of potential relapse of cancer were not included in the analysis.

Standard Study Treatment protocols

Both arms of the study were the standard regimes used in our department. Standard treatment at the time of the study was weekly Cisplatin 40mg/m2 chemoradiotherapy plus 70Gy in 35 fractions. Cetuximab in the doses below is the NICE approved schedule for patients unable to receive a platinum agent with radiotherapy.

Arm A

Prophylactic PEG placement for all patients (as standard departmental protocol)

Pre Radiotherapy Dental Assessment for all patients (as standard departmental protocol)

Pre - Chemotherapy FBC, U+E, LFT for each cycle

Cisplatin 40mg/m2 over 2 hours plus1 litre normal saline over 2 hours as pre and post hydration (as per standard local protocol) delivered weekly during radiotherapy, 70Gy in 35 fractions over 47 days. Antiemetics 8mg ondansetron i.v. and 8 mg dexamethasone i.v. Post treatment oral antiemetics ondansetron 8 mg twice as a day for 3 days plus dexamethasone 8 mg once a day for 3 days.

weekly review during radiotherapy by specialist radiographers((standard management))

weekly review during radiotherapy by clinical oncology medical team in on -treatment review clinic (standard management)

weekly review after radiotherapy by Head and Neck cancer clinical nurse specialist in post treatment toxicity review clinic for 3 weeks (standard management)

Post treatment review at 6 weeks following completion of radiotherapy in joint ENT/oncology clinic (standard management)

Post treatment scan (CT, MRI or PET) at 10-12 weeks following completion of treatment (standard management)

Monthly review in joint ENT/oncology clinic (standard management)

Arm B

Prophylactic PEG placement for patients receiving oral cavity irradiation, large irradiated volume, pre-treatment dysphagia, significant pre treatment weight loss(as standard departmental protocol)

Pre Radiotherapy Dental Assessment for all patients (as standard departmental protocol)

No routine blood tests

Erbitux (cetuximab) 400 mg/m2 over 2 hours1 week prior to radiotherapy followed by Cetuximab 250 mg/m2 over 1 hour weekly during radiotherapy, 70Gy in 35 fractions over 47 days. Pre medication prior to Cetuximab of 50mg diphenhydramine and 8mg i.v. dexamethasone.

weekly review during radiotherapy by specialist radiographers (standard management))

weekly review during radiotherapy by clinical oncology medical team in on -treatment review clinic (standard management)

weekly review after radiotherapy by Head and Neck cancer clinical nurse specialist in post treatment toxicity review clinic for 3 weeks (standard management)

Post treatment review at 6 weeks following completion of radiotherapy in joint ENT/oncology clinic (standard management)

Post treatment scan (CT, MRI or PET) at 10-12 weeks following completion of treatment (standard management)

Monthly review in joint ENT/oncology clinic (standard management)

Inclusion criteria

Patients were eligible for inclusion if the following criteria were met:

a) Patients with Squamous Cell Carcinoma of the Oropharynx, Larynx and Hypopharynx suitable for radical primary treatment with chemoradiotherapy in the opinion of treating clinical oncologist

Radiotherapy Schedule prescibed to be 70Gy in 35 fractions 5 fraction per week

b) TNM Stage 3 or 4 (7th editiion)

c) Patient considered sutable to recieve cisplatin therapy in the opinion of treating clinical oncologist

d) Age 18-70

e) Expected survival greater than 6 months·

f) Patient able to give informed consent

g) Haematological Parameters at study entry: -

·Haematological Parameters at study entry: -

· Blood cell counts:

Absolute neutrophils > 1.5 x 10^9/L

Platelets > 100 x10^9/L

Haemoglobin > 10 g/dl (may be correcetd by transfusion where appropriate)

- Renal function:

  EDTA-based glomelular filtration rate of > 50 mL/min or a cockcroft gault calculated GFR of > 60 mL/min.

- Hepatic functions:

  Serum bilirubin within normal limits.

  or AST or ALT < 1.5 x ULN with alkaline phosphatase < 2.5 x ULN.

h) Female patients potentially able to child bear should use an approved contraceptive method (IUD, birth control pills or barrier device) during and for 3 months after the study. All male patients should take adequate contraceptive precautions during and up to 2 months after the study

Exclusion Criteria

Palliative Radiotherapy

Accelerated Radiotherapy

Prior Radical Surgery for Primary Squamous Cell Carcinoma of the Head and Neck (neck disection is allowed)

Treatment within the last 4 weeks with any investigational drug.

Presence of distant metastases.

Evidence of uncontrolled infection.

Mental condition rendering the subject unable to understand the nature, scope and possible consequences of the study.

Neoadjuvant chemotherapy for squamous cell carcinoma of the head and neck prior to study entry.

Preexisiting peripheral sensory neuropathy

Drug supply

Cetuximab for this study was supplied by Merk Serono from trial stock. The Cisplatin was supplied from general stock the pharmacy department at New Cross Hospital Wolverhampton

.Dose modifications and treatment alterations

Cetuximab

Skin toxicities

If a subject experiences a grade 3 skin toxicity (as defined in the US National Cancer Institute's - Common Toxicity Criteria [NCI-CTC] version 3), cetuximab therapy may be delayed for up to two consecutive infusions without changing the dose level. For grade 1 or 2 acne-like rash treatment with topical antibiotics (e.g. benzoylperoxide, erythromycin) or systemic antibiotics (e.g. oral tetracyclines such as doxycycline 100 mg od) should be considered. Patients with grade ≥ 3 reactions should be referred to the dermatologist for advice and management. If pruritus occurs an oral antihistamine is

advised. In case of dry skin the use of emollient creams is beneficial. Fissures may occur in dry skin and topical dressings are helpful. If the toxicity resolves to grade 2 or less by the following treatment period, treatment may resume. With the second and third occurrences of grade 3 skin toxicity, cetuximab therapy may again be delayed for up to two consecutive weeks with concomitant dose reductions to 200 mg/m^2 and 150 mg/m^2, respectively. Cetuximab dose reductions are permanent. Subjects should discontinue cetuximab if more than two consecutive infusions are withheld or a fourth occurrence of a grade 3 skin toxicity occurs despite appropriate dose reduction see figure 1.

However, if in the opinion of the investigator the discontinuation of cetuximab is considered necessary, the subject should be withdrawn immediately.

The dose of cetuximab will be adjusted for cetuximab-related grade 3 skin toxicities only.

Allergic/hypersensitivity reactions

In each case of allergic/hypersensitivity reaction, the investigator should implement treatment measures according to the best available medical practice. Based on previous experience with cetuximab allergic/hypersensitivity reactions, the treatment guidelines as described in table 2 may be applicable.

Re-treatment following allergic/hypersensitivity reactions:

Once a cetuximab infusion rate has been decreased due to an allergic/hypersensitivity reaction, it will remain decreased for all subsequent infusions. If the subject has a second allergic/hypersensitivity reaction with the slower infusion rate, the infusion should be stopped, and the subject should be removed from the study. If a subject experiences a Grade 3 or 4-allergic/hypersensitivity reactions at any time, cetuximab should be discontinued.

Cisplatin

Heamtological toxicity

Other reasons for cetuximab discontinuation

If a subject develops an intercurrent illness (i.e., infection) that, in the opinion of the investigator mandates interruption of cetuximab therapy, that intercurrent illness must resolve within a time frame such that no more than two consecutive infusions are withheld. After the interruption of treatment, the subject will continue with a cetuximab dose of 250 mg/m^2 at subsequent visits or the last dose before the interruption if there have been previous dose reductions.

If therapy must be withheld for a longer period of time, the subject will be removed from the study treatment. In special cases, the investigator may request that the patient continues to receive cetuximab (the investigator must ask permission from the Investigator-Sponsor).

Cisplatin

Haematological Toxicity

Suspend further cisplatin administration until platelet count greater than 100 x 10^9 .

Suspend further cisplatin administration until neutrophil count greater than 1.5 x 10^9

Renal Toxicity

Grade 1 toxicity suspend further cisplatin administration until recovery

Grade 2 toxicity stop chemotherapy continue treatment with radiotherapy alone

Changes in the Conduct of the Study or Planned Analyses

The study was a pilot study to see if a randomized study investigating the effects of cisplatin or Cetuximab chemoradiation on quality of life would be practical and of value.

Initially the protocol required quality of life assessments at fixed time points however it proved impossible to schedule the quality of life questionnaire assessments tightly especially as many patients chose the option of taking the quality of life questionnaire home to complete and return rather than complete the form in the clinic environment. An amendment provided wider time period fort the quality of life assessments to be completed as per protocol.

The protocol did not require routine blood tests prior to Cetuximab delivery. However FBS, U+E and LFT's were sometimes requested unnecessarily by the nurses in the chemotherapy suite as routine test. As these blood tests were performed in error those blood tests taken 24hours prior to Cetuximab delivery when the requesting of the blood test was not prompted by clinical review were excluded from the analysis.

The Protocol demanded that the time spent by the head and neck clinical nurse specialists, dieticians and speech and language therapist be analyzed by group as routine intervention, and unplanned intervention. However during data analysis it proved impossible to distinguish between what was routine and what was unplanned. The time spent with the patients for each health care professional group was therefore analyzed as one total rater than routine and unplanned. The assumption being that for head and neck clinical nurse specialists, dieticians and speech and language therapists the routine care would be equal in arm A and arm B so any differences would be due to differences in toxicity profiles between the two groups

The design of the study was to attempt to quantify the differences in resources required to manage different toxicity profiles for Cetuximab radiotherapy and Cisplatin radiotherapy following standard management protocols. This meant that the patients participating in the study came in to contact with many health care professional during their care. While the members of the head and neck clinical team were fully aware of the requirement to document the time taken for health care interventions with the patients on the study, the junior doctors and non specialist radiographers did not follow instructions on the patient notes and radiotherapy cards to document the time spent with the patients. Therefore a estimated standard "time tariff" was applied to all interventions/interactions made by non specialist head and neck team health care professionals. This was applied to both arms of the study and details were as follows. All interactions between patients and junior doctors, non head and neck team nursing staff and radiographers outside the routine assessment clinics and routine delivery of radiotherapy care was classed as non routine/emergency care.

- Full History = 10 minutes
- Full Examination= 10 minutes
- Specific Individual Symptom review = 10 minutes
- Requesting a test and follow-up up result =10mintes (5 minutes to request and/or 5 minutes to review the result)
- Telephone call for advice= 5 minutes
- Writing a prescription = 5 minutes

In modern health care practice many health care professionals have extended roles so it was impractical to divide these interventions in to doctor, nurse, radiographer and therefore impossible to apply an estimated cost in pounds for the time spent with the patient. The time spent with the patient for non routine care by non head and neck team professionals was therefore calculated as a total for each patient. All interactions by non head and neck team health care professions with the patients in the study were classified as unplanned. (As if the interaction/intervention had been planned it would have been scheduled with a member of the specialist head and neck team)

Medical interventions and investigations for pre existing conditions or investigations of second primary cancers or potential recurrences were not included in the analysis.

Initially the protocol stated patients with a heamoglobin >12g/dl were eligible. This was an error in protocol writing and should have read 10g/dl. This was corrected in an ammendment.

The internal market for the N.H.S. made costing in direct monitary value very difficult as costs would vary as to who was paying for the service. The overall cost for the treaments in this study were therefore taken as the cost to the PCT which could be defined more robustly

Costing procedures

Costing activity proved more difficult than expected as there was not a single price for activity and cost " to whom" was often difficult to define within NHS structure i.e. the cost to the hospital would be different to the cost to the PCT for the same event/test. The following costing structures were used.

- Drug prices were taken from the BNF 60, September 2010.
- Unplanned attendances at hospital were each assigned a single HRG code by the chief investigator CZ24P (complex/major head and neck disorder with intermediate comorbidity/complication) or CZ24Q(complex/major head and neck disorder with no comorbidity/complication) and the cost for this episode taken as the local HRG code tariffs.
    - CZ24Q length of stay = 0- less than 3 days = £695
    - CZ24Q length of stay = 3 or more days = £2780
    - CZ24P length of stay = 0- less than 3 days = £832
    - CZ24P length of stay = 3 or more days = £3328
- Dietary supplement prices were taken from nutridrinks.co.uk
- Time spent with Clinical Nurse Specialist, Dietician, Speech and language therapist, and direct nursing time during routine chemotherapy delivery were expressed as a mean time in minutes for both arms of the study. This was not- translated in to a cost in pounds sterling as different individuals in the same team fulfilling the same role managing patients in this study may be on slightly different pay scales due to seniority which made costing the role less robust.
- Time spent on non routine care with non Head and Neck Team members was expressed as a mean time in minutes for both arms of the study. This was not translated in to a cost in pounds sterling.
- Costs for Xrays and CT scans were obtained from the Clinical Director of Radiology at New Cross Hospital, Dr S Vydianath at £50 for plain Xrays and £200 for a single area CT
- Costs for laboratory tests heamatology clinical chemistry and Microbiology were obtained from Graham Danks, New Cross Hospital Wolverhampton. The laboratory costs provided were the process the hospital charges for tests from external sources as internal costing structure was not available.

Removal from Assessment

A the study was divided in to 3 study periods, "On treatment", "Acute Phase" and "Late Phase" patient data was analysed for all treatment periods completed

Patients were withdrawn from the study phase if recurrence occurred during the study period a second primary was discovered during the study period, patients were unable or unwilling to comply with the follow-up shedule during that phase. Patients died during the study period

Treatment Compliance

All breaks in radiotherapy treatment were documented for patients in both arms of the study. Chemotherapy/Immunotherapy dose intensity was documented for patients in both arms of the study.

As the investigational products were intravenous, compliance from the patient was 100% as supported by the clinical staff within the hospital. Records of treatment are detailed on patient charts and notes as per standard hospital practice. Supportive drugs such as anti emetics were supplied to the patient following chemotherapy
The delivery antiemetic compliance was informally assessed by asking the patients at the weekly medical review. Compliance was not formally assessed.

Data Quality Assurance

Monitoring was conducted internally by the R&D Directorate on behalf of the Sponsor, The Royal Wolverhampton Hospitals NHS Trust. Monitoring of the study was conducted to ensure the quality of the data and to ensure the collection of accurate, consistent, complete and reliable data. The study files were reviewed to ensure all documents were in place and filed accordingly. The core documents were reviewed to ensure all appropriate information was given. Training was documented appropriately and data security ensured. At set time points the study documents were reviewed to ensure the correct approved documents were in use at the right time, patient recruitment, eligibility criteria, consent, and SAEs against source data were checked.

Protocol Deviations

1 patient (EBRT 2) was entered in to the study randomised with a haemoglobin level of 10.8g/dl prior to the protocol amendment correcting the haemoglobin eligibility criteria for >12g/dl to >10g/dl. This patient suffered no ill effects as a result of this and would have received the same standard therapy if they had not been entered into the study. The patient was therefore no withdrawn from the study and the data was therefore included in the analysis

1 patient (EBRT 9) was randomised in to the study but prior to treatment it was noted that the patient was older than 70 years of age and therefore not eligible for entry in to the study. The patient was therefore withdrawn from the study prior to treatment delivery and the randomisation envelope replaced.

1 patient (EBRT 8) was randomised and entered in to the study however it was noted after treatment during the data analysis that the patient was 74 years old and therefore should not have been entered in to the study . However the patient was very physiologically and physically fit and in the opinion of the chief investigator had received the same treatment that they would have received if they had not been entered in to the study and therefore the patient was not excluded from the study and data was included in the analysis

One patient (EBRT 19)randomised to Arm A Cisplatin Radiotherapy refused pre treatment PEG placement when this was arranged. PEG was placed during radiotherapy when toxicity developed
One patient (EBRT 11) refused to attend New Cross Hospital for follow up visits preferring to attend the Head and Neck team clinic joint clinic at the unit closer to their home. Folllow-up data continued to be collected for the individual by investigators involved in the study working in the joint oncology clinic on that site

Baseline quality of life forms were not collected for EBRT 11 and 18 as these patients were given the forms to take home and complete but these patients did not return the forms to the investigators. End of treatment. Quality of Life form was missed in EBRT 10 as the patient was an inpatient and therefore did not attend outpatient clinic. Quality of life forms at the end of treatment, 6 weeks post treatment and 6 months post treatment were not collected for EBRT 13.

Adverse events

This was a post marketing pilot study. Common, expected and well documented side effects of treatment for Cisplatin and Cetuximab detailed in the SPC for these drugs were not reported in the study as adverse events. (e.g. acneform rash, hypomagnesia, nausea, vomiting, anaemia, myelosupession)
Common, expected and well documented side effects of radiotherapy (e.g. erythema, moist desquamation, mucositis, dysphagia, xerostomia) were also not reported as adverse events.

Serious Adverse Events

There was 1 death following treatment (EBRT 5) due to pneumonia, this was categorised as being likely to be related to treatment (radiotherapy) is an expected complication so not unexpected.

Unplanned hospital admission due to expected side effects of chemoradiotherapy was an outcome measure for the study so is reported in the results section.

Trial results

All patients were of performance status 0 or 1 at entry to the study

1 Patient Characteristics and Treatment Delivered

	Cetuximab		Cisplatin	
Sex	3 Female	7 Male	3 Female	7 Male
Age	Median=60		Median=59.5	
	44-66years		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 Cetuximab arm 1 too ill to attend 1 required second mould due to weight loss • both episodes uncompensated		5 Cisplatin arm 3 too ill to attend 1 PEG fitting (patient refused PEG pre treatment) • all above compensated by bd fractions) 1 treatment suspended due to toxicity at 66gy • uncompensated	
Concomitant Drug Dose intensity delivered	88.75%		90%	
Radiotherapy dose delivered	100% of patients received prescribed dose of 70Gy		95% of patients received prescribed dose of 70Gy 5% (1 patient) received 66Gy. Treatment curtailed due to acute toxicity	

2) Routine nursing time for delivery of concomitant drug treatment - (pre trial time and motion study)

Cisplatin (n=3): mean = 133 minutes/patient
Cetuximab (n = 3): mean = 68 minutes/patient

preparation time from aseptic suite to delivery at the chemotherapy suite was the same for both treatments expect Cetuximab required and additional 10 minutes cleaning time for the aseptic area in pharmacy per patient.

3) Number of patients available for Assessment

3a) Treatment Phase

All patients completed included in the study completed the treatment phase

3b) Acute phase

2 patients were withdrawn from the study after the completion of radiotherapy.

1 Cisplatin Arm – found to have second synchronous primary after randomisation (EBRT 3)
1Cetuximab arm – died of pneumonia during acute phase (EBRT 5)

3c) Late phase

1 patient was withdrawn from the study after the acute phase
1 Cisplatin arm – Developed Metastatic disease during Acute Phase

17 patients completed the follow up /late phase of the study

4) Cost of Treatment : Drugs

4a) Mean Cost of Chemotherapy Prescription per patient (plus antiemetics and fluids)

Cisplatin Plus Radiotherapy :£361.47 per patient

Cetuximab Plus Radiotherapy: £5142.95 per patient

4b) Mean Cost of Supportive Medications (non chemotherapy prescription)

Cisplatin Plus Radiotherapy, Acute Phase (n = 9) : £720.89

Cetuximab Plus Radiotherapy, Acute Phase (n = 9) : £608.90

Cisplatin Plus Radiotherapy, Late Phase (n = 8) : £248.65

Cetuximab Plus Radiotherapy, Acute Phase (n = 9) : £172

Cisplatin Plus Radiotherapy, Total Mean £969.54

Cetuximab Plus Radiotherapy Total Mean £780.90

4c) Total Drug Cost/Patient

Cisplatin Plus Radiotherapy, £361.47+ £969.54 =1331.01

Cetuximab Plus Radiotherapy £5142.95 + £780.90 =5923.85

5a) Inpatient Admissions During The Acute and Treatment Phase Of The Study Period

5ai) 3ai) Cisplatin Arm

5/10 patients required admission during the treatment and acute phase of treatment.

2 patients were admitted twice

2 and 5 nights (both admissions for nausea and vomiting secondary to cisplatin)
2 and 8 nights (for nausea and vomiting and pneumonia)

3 patients were admitted overnight on one occasions

22 nights (pneumonia)
11 nights (mucositis and nausea)
8 nights (hypomagnesia)

= total of 63 nights

Additionally 4 days case admissions were required

2 for 2 unit blood transfusions
1 for iv antibiotics for neutropenic fever (patient refused admission)
1 for iv fluids

5aii) Cetuximab Arm

2/10 patients required admission during the acute and treatment phase of treatment.

1 patient was admitted twice for

13 and 21 nights(both admissions for management of dysphagia and mucositis.)

1 patient was admitted on one occasion

3 nights admission (patient died of pneumonia,)

= total of 37 nights

Additionally 1 day case admissions was required

1 for iv fluids

5b) Cost of admissions (Acute and treatment phase)

- Cisplatin
  - 7 admissions HRG code=CZ24P x7
  - 4 day case HRG code=CZ24Q x3
    HRG code=CZ24P x1
  - mean=£2788.09/patient
- Cetuximab
  - 3 admissions HRG code=CZ24P x3
  - 1 day case HRG code=CZ24Q x1
  - mean=£1137.79/patient

6 Dietary suppliments

6a) Cost of Dietary Supplements

6ai) Acute phase

- Cisplatin (n=9) = £1115.62/patient
- Cetuximab (n=9) = £909.6/patient

6aii) Late phase

- Cisplatin (n=8) = £1512.5/patient
- Cetuximab (n=9) = £634/patient

6aiii) Total

- Cisplatin = £2628.12/patient
- Cetuximab = £1543.60/patient

7 a Additional Outpatient Non-Routine /Emergency Care Provided in the Treatment and Acute Phase (excludes SALT, Dietician, Consultant and ENT clinical nurse specialist which are evaluated separately)

	Cisplatin Arm 10 patients		Cetuximab Arm 10 patients	
	Total Number of Non Routine Care Minutes	Number of additional contacts	Total Number of Non Routine Care Minutes	Number of additional contacts
SHOa	600	20	215	9
Registrar	65	6	130	8
Therapy Radiographer	65	11	20	4
Nursing staff	340	17	115	7
Total	1070minutes	54contacts	480 minutes	28contacts

Total estimated non routine care during the acute phase for non head and neck team personnel:
Cisplatin (n = 10) mean = 107 minutes/patient
Cetuximab (n=10) 48 minutes /patient
t test p = 0.01

8 Total Outpatient Care Provided by Head and Neck Team

	Acute and treatment Phase additional time in minutes/patient		Late Phase additional time in minutes	
	Cisplatin	Cetuximab	Cisplatin	Cetuximab
Dietician	96.1mins	93.5mins/	46.5	24
t test p=			0.29	
Head and Neck CNS	114.2	97	44	28
t test p=			0.3	
Speech and Language therapy	58.3	17	64.3	32.7
t test p=			p=0.27	

There was no significant difference in time spent in care in outpatient between the two arns of the study for dietician, SALT or head and neck clinical nurse specialist input

9 Number and Estimated Cost of Investigations during treatment

9a Radiology

	Cisplatin		Cetuximab	
Acute and Treatment Phase	No. Plain Xrays = 14	£700	No. Plain Xrays =7	£350
	No. CT scans = 1	£200	No. CT scans = 0	
Estimated Cost/patient n = 10	£90		£35	

Late Phase	No. Plain Xrays = 1	£50	No. Plain Xrays = 3	£150
	No. CT scans = 0		No. CT scans = 0	
Estimated Cost/patient	n = 8 £6.25		n=9 £16.70	

9b) Laboratory tests

9bi) Treatment and Acute Phase (includes data for all patients completing treatment

Test	Test required to management of toxicity or anticancer treatment	Cisplatin		Cetuximab	
		No Tests	Estimated Cost using external pricing stucture	No. Tests	Estimated Cost using external pricing stucture
FBC	Toxicity	67	£725.40	33	£193.05
	Treatment	57		0	
U+E	Toxicity	54	£565	34	£170
	Treatment	59		0	
LFT	Toxicity	32	£440	13	£65
	Treatment	56		0	
Bone Profile	Toxicity	16	£225	18	£90
	Treatment	29		0	
Serum Magnesium	Toxicity	13	£65	15	£75
	Treatment	0		0	
C-Reactive Protein	Toxicity	15	£75	15	£75
	Treatment	0		0	
Blood Culture	Toxicity	8	£60	6	£45
	Treatment	0		0	
MSU m.c.s.	Toxicity	1	£7.50	2	£7.50
	Treatment	0		0	
Swab m.c.s.	Toxicity	5	£37.50	4	£30
	Treatment	0		0	
Group and Save (blood group)	Toxicity	2	£27.60	2	£27.60
	Treatment	0		0	
Cross matched unit of blood	Toxicity	10	£1248.50	4	£499.40
	Treatment	0		0	
Anticoagulation studies	Toxicity	5	£26	2	£10.40
	Treatment	0		0	
Other microbiology	Toxicity	2	£15	1	£7.50
	Treatment	0		0	
Other Clinical Chemistry	Toxicity	12	£70	34	£120
	Treatment	0		0	
Total Cost	Total	443	£3587.50	183	£1415,40
	Total/patient n=10		£358.75		£141.54

9bii) Late Phase

Test	Test required to management of toxicity or anticancer treatment	Cisplatin		Cetuximab	
		No Tests	Estimated Cost	No. Tests	Estimated Cost t
FBC	Toxicity	2	£11.70	8	£46.80
U+E	Toxicity	1	£5.00	8	£40.00
LFT	Toxicity	0	0	4	£40.00
Bone Profile	Toxicity	0	0	2	£10.00
C-Reactive Protein	Toxicity	0	0	2	£10.00
Swab m.c.s.	Toxicity	1	£7.50	0	0
Other Clinical Chemistry	Toxicity	3	£15.00	10	£50.00
Total Cost	Total	7	£39.20	34	£196.8
	Total/patient n=8		£4.90		£21.86

Patients receiving cisplatin and radiotherapy required double the radiology and laboratory investigations during the acute phase of treatment than those who received treatment with Cetuximab and radiotherapy. Radiology : 15 investigations for patients treated with Cisplatin vs 7 for those treated with Cetuximab. Laboratory : 443investigations for patients treated with Cisplatin vs 183for those treated with Cetuximab.

As the costs in the table above were not those to the treating organisation they are not appropriate for use in the overall costing for treatment. The cost for tests to the PCT are included in the HRG code tariffs for admission and day case treatments.

10)Local recurrence and Survival

At the censor date of 22nd August (minimum follow-up 21 months).
Overall Survival . 80% in the Cisplatin arm vs 50% in the Cetuximab and radiotherapy arm. Log Rank p=0.332
Disease Free Survival . 80% in the Cisplatin arm vs 40% in the Cetuximab and radiotherapy arm. Log Rank p=0.097
Local Recurrence Free survival. 100% in the Cisplatin arm vs 50% and radiotherapy arm Overall Log Rank p=0.014

11) Quality of life

There was no significant difference in quality of life scores for Functional Score, Symptom Core, Global Quality of life score or Head and Neck Symptom score between to two arms of the study at any of the time points in the study, baseline, end of treatment, 6 weeks post treatment or 6 months after completion after treatment .

There was a statistically significant difference (χ^2) in patient reported use of PEG between the cisplatin and Cetuximab arms at 6 months following completion of treatment.

	Base line : Pre treatment		End of Treatment		6 weeks Following completion of radiotherapy		6 months following completion of radiotherapy	
	Cisplatin	Cetuximab	Cisplatin	Cetuximab	Cisplatin	Cetuximab	Cisplatin	Cetuximab
Functional Score mean (+/- standard deviation)	74.4 (+/- 19.15)	82.9(+/- 22.2)	43.9(+/- 24.8)	59.7(+/- 28.1)	67.4(+/- 27.0)	69.8(+/- 19.7)	53.8(+/- 36.4)	73.6(+/- 26.5)
t - test (unpaired, 2 tailed) p=	0.72		0.23		0.82		0.23	
Symptom score (+/- standard deviation)	18.9 (+/- 15.1)	22.8(+/- 23.9)	53.2(+/- 23.1)	36.2(+/- 21.8)	31.2(+/- 20.1)	25.9(+/- 15.0)	37.1(+/- 31.2)	20.5(+/- 14.7)
t - test (unpaired, 2 tailed) p=	0.69		0.12		0.62		0.20	
Global QoL	60.3((+/- 39.5)	64.9(+/- 31.5)	40.83(+/- 24.7)	41.8(+/- 30.4)	58.3(+/- 20.8	61.1(+/- 16.2)	45.8(+/- 31.5)	66.6(+/- 21.4)
t - test (unpaired, 2 tailed) p=	0.79		0.94		0.76		0.15	
Head and Neck Symptom score	22.9(+/- 21.9)	20.4(+/- 24.1)	71.1(+/- 18.1)	45.6(+/- 18.3)	42.5(+/- 22.7)	28.4(+/- 14.6)	48.3(+/- 30.8)	25.8(+/- 23.7)
t - test (unpaired, 2 tailed) p=	0.83		0.009		0.14		0.13	
Peg Use (number/population)	0/9	0/9	9/10	4/8	8/9	4/9	5/8	1/8
χ^2 p=	1		0.06		0.26		0.04	
Nutritional supplement use	3/9	0/9	10/10	7/8	6/9	5/9	4/8	3/8

Conclusions

This was a small pilot study to investigate whether a study to investigate choice of treatment Cisplatin or Cetuximab plus radiotherapy on quality of life and functional outcomes would be viable. While the study methodology did not allow costs to the individual organisation to be calculated robustly, the cost of concomitant Cetuximab plus radiotherapy (drug cost plus dietary supplements plus cost of unplanned admission =£7824.35) still appeared to be substantially more than that compared to the cost of cisplatin and radiotherapy (drug cost plus dietary supplements plus cost of unplanned admission £5777.68) however when one takes in to account use of manpower resource and investigations involved in managing the toxicity of treatment these differences are not so great to preclude development of an academic study within the NHS as patient treated with cisplatin and radiotherapy were more likely to be admitted during treatment and need more intense management for the treating organisation. (see table)

Differences in PEG use at 6 and 12 months suggest a significant improvement in functional outcomes with the use of Cetuximab compared to cisplatin radiotherapy which deserves further investigation. Quality of life was not significantly different between the two arms in this study but there

are small numbers and the hint of a trend to improve at 6 months for those in the Cetuximab arm should also be investigated further.

Of concern however, is the significantly increased local recurrence rate in the Cetuximab arm in this study although the study was not designed to investigate differences in recurrence rates or survival and this was not an outcome measure for the study.

Quality of life and functional effects of late toxicity should be investigated in a larger study which should also be powered to investigate differences in local recurrence between cisplatin and Cetuximab

Total Resources Implications by Treatment

	Cisplatin		Cetuximab	
Drug Cost of Concomitant Chemo/immunotherapy	£361.47/patient		£5142.95/patient	
Supportive Medications (excluding antiemetic included above)	Acute Phase £720.89	Late Phase £248.65	Acute Phase £608.90	Late Phase £172
	Total £969.54		£780.90	
Dietary Supplements	Acute Phase £1115.62	Late Phase £1512.50	Acute Phase £909.60	Late Phase £634
	Total £2628.12		Total £1543.60	
Cost of unplanned Admission	£2788.09/patient		£1137.79/patient	
Number of Radiological Investigations	Acute Phase 15	Late Phase 1	Acute Phase 7	Late Phase 3
Number of Laboratory Investigations	Acute Phase 443	Late Phase 7	Acute Phase 183	Late Phase 34
Approximate Number of Additional Minutes of care by Non Head and Neck Team Personnel (Acute Phase)	107mins/patient 5.4 contact/patient		48mins/patient 2.8 contact/patient	
Number of Minutes of care by Head and Neck CNS	Acute Phase 114.2mins/patient	Late Phase 44 mins/patient	Acute Phase 97 mins/patient	Late Phase 28 mins/patient
Number of Minutes of care by Dietician	Acute Phase 96.1mins/patient	Late Phase 46.5 mins/patient	Acute Phase 93.5 mins/patient	Late Phase 24 mins/patient
Number of Minutes of care by SALT	Acute Phase 58.3 mins/patient	Late Phase 64.3 min/patient	Acute Phase 17 mins/patient	Late Phase 32.7 min/patient

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Appendix 1 Protocol plus CRFs

Cost Analysis Of Cetuximab (Erbitux) Plus Radiotherapy (ERT) Versus Concomitant Cisplatin Plus Radiotherapy (CRT) Within An NHS Oncology Unit (New Cross Hospital Wolverhampton): A Pilot Study

Chief Investigator
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Sponsor - Royal Wolverhampton Hospitals Trust

Cost analysis of cetuximab (Erbitux) plus radiotherapy (ERT) versus concomitant cisplatin plus radiotherapy (CRT) within an NHS Oncology Unit

1.Introduction

1. 1Background

Cetuximab given concomitantly with radiotherapy has been shown to significantly improve overall survival for patients with locally advanced squamous cell carcinoma of the head and neck, with data showing a 57% overall survival at 3 years compared 44% in patients treated with radiotherapy alone, p=0.02. [1]. This study confirmed the addition of Cetuximab to radiotherapy improved local control and overall survival in patients with locally advanced carcinoma of the head and neck. Cetuximab and radiotherapy is considered an option for radical potentially curable therapy for these patients.[2]. Cetuximab has been approved by the F.D.A. in the U.S.A. for this indication. Meta analysis has also indicated that chemo radiation with cisplatin appears to confer an overall survival advantage of around 11% when compared to radiotherapy alone but this is associated with a significant added acute and late toxicity. [3] A recent meta analysis has questioned the value of Cisplatin based chemoradiotherapy in the over 70's, the therapeutic ratio of therapy being reduced by severe toxicity and treatment related mortality in the elderly. [4]. Elderly patients have also been identified at being at higher risk of late toxicity following cisplatin-based chemoirradiation. [5]While Cetuximab given in conjunction with radiotherapy increases acute skin toxicity when compared to radiotherapy alone, this is reported to be manageable and there is no reported increase in late toxicity or treatment related mortality.[1] However there is no direct clinical randomized trial comparing outcomes form cisplatin based chemoradiotherapy and Cetuximab given concomitantly with radiotherapy although indirect comparisons between randomized trials suggest there is a similar gain in overall survival from either approach when compared to radiotherapy alone

1.1a Management of acute side effects during radiotherapy

Cisplatin related adverse events often require considerable clinical follow-up (including hospitalization). Local audit has suggested a 19.6% incidence of mild to moderate renal dysfunction (grade 1 and 2) and 21.6% incidence of severe (grade 3-4) neutropenia with a 13.7% admission rate with neutropenic fever. [6] This is similar to toxicity rate reported in the literature. From a study investigating chemoirradiation for carcinoma of the larynx where 180 patients received concomitant cisplatin with radical radiotherapy 47% of patients were found to develop grade 3 or 4 neutropenia and 4 % developed severe (grade 3-4) renal toxicity. [7]

Cisplatin based chemoradiotherapy for head and neck cancer is associated with increased mucositis and dysphagia when compared to treatment with radiotherapy alone.[8] Local practice is to insert a percutaneous endoscopic gastrostomy feeding tube (PEG) prior to the delivery of concomitant cisplatin and radiotherapy for head and neck cancer to manage this. Local audit has indicated that if a P.E.G. tube is not inserted for patients undergoing chemoradiotherapy patients loose significantly more weight during radiotherapy and are therefore at risk if the complications of malnutrition. Patients without a PEG are also significantly more likely to have at least one emergency admission [local audit data],during treatment compared to those patients being treated with radiotherapy alone due to the complications of cisplatin therapy i.e. mucositis, neutropenia and renal dysfunction. Local

audit has also shown that patients who do not have a PEG inserted if the local criteria for PEG insertion are met are significantly more likely to have an unplanned admission during the course of their radiotherapy. Local audit has shown 70 % of patients undergoing chemoradiotherapy for head and neck cancer still require feeding via PEG at 3 months following treatment and 14% are still supplemented by artificial feeding at 12 months following radiotherapy due to prolonged dysphagia. This is consistent with functional outcomes reported in published literature. The Cleveland clinic, Ohio, reports 77% of patients requiring PEG feeding at 3 months following cisplatin chemoirradiation and 17% at 12 months requiring supplementary feeding (8% still PEG reliant) [9]

Routine local practice has been to arrange for prophylactic gastrostomy placement prior to radiotherapy for patients fulfilling the following criteria

patients receiving chemoradiotherapy

patients relieving accelerated radiotherapy (see trial exclusion criteria)

significant weight loss (>10%) or dysphagia (anything other than normal swallowing function) prior to radiotherapy

oral cavity irradiation (except unilateral oral cavity irradiation)

large irradiated volume i.e. nasopharynx

Local Audit revealed that patients who met the above criteria and did not receive prophylactic PEG placement were significantly more likely to require emergency admission than Patients who did not meet the above criteria and did not receive PEG placement. Patients who did undergo PEG placement (usually patients who received a PEG pre reconstructive surgery) and did not have any of the above risk factors were not dependent upon the PEG for feeding during radiotherapy or during the recovery period (unpublished data).
The Oncology department only has 22 inpatient beds for all oncology admissions therefore inpatient resources are limited. The policy for prophylactic PEG placement was developed to ensure that patients can safely be treated as outpatients for the duration of their treatment and immediate post therapy period.
In practice the majority of patients with stage 3 or 4 squamous eall carcinoma of the head and neck requiring radical non surgical therapy will fulfil the criteria for PEG insertion due to pre treatment weight loss, volume of irradiation or oral cavity irradiation. (accelerated radiotherapy is a trial exclusion).
If patients required artificial feeding during radiotherapy when a PEG has not been placed pre-treatment an NG tube is usually inserted in the first instance. If it is apparent that artificial feeding will be required for more than 3 weeks or if the patient tolerates NG tube placement poorly then a PEG tube will be placed during treatment. Any breaks in treatment are corrected following departmental guidelines with twice a day fractionation (each fraction greater than 6 hours apart) so overall treatment time is not prolonged.

1.1b Rationale For Performing The Study

While the drug cost for cetuximab (approx £ 5000 total for cetuximab alone) when used concomitantly with radiotherapy is higher than the drug cost of cisplatin (approx £500 in total for cisplatin plus antiemetics alone) when used concomitantly with radiotherapy, it is possible that some or all of the additional costs of ERT are off-set when follow-up analysis of cisplatin adverse event costs have been considered. Prophylactic PEG placement should also be considered an adverse event cost for cisplatin chemoirradiation as in our unit it is considered essential to prevent emergency admission for NG feeding or for the consequences of dehydration/malnutrition during radiotherapy. Costing data is essential for the managed entry of new drugs into clinical practice for NHS Trusts and Cancer Networks in the UK. Also the development of oncology unit/cancer network Local Delivery Plans require cost data to assess the impact of new interventions upon the overall capacity of the Unit to deliver services. This study aims to assess this as Cetuximab therapy may release resources in terms of the direct costs (i.e. extra clinic staff time to treat cisplatin related AE's) while potentially providing the same overall survival advantage. No indirect or intangible costs will be considered in this study i.e. cost of the management of recurrent disease which will be assumed to be equal in both arms. Both arms of the study will use similar radiotherapy fractionation schedules of 70Gy in 35 fractions, 5 fractions per week, patients in whom accelerated fractionation schedules are thought to be appropriate will not be eligible for this study. It is therefore likely that the majority of patients in this study will be receiving treatment of stage 3 or 4 carcinoma of the oropharynx. 60% of patients in Bonner study [1]comparing ERT versus radiotherapy alone were receiving treatment for oropharyngeal carcinoma so the results of this study confirming an overall survival advantage for the use of Cetuximab are directly applicable to this group of patients.

Studies combining Cetuximab, cisplatin and radiotherapy have been found to be toxic in pilot studies although randomized phase 3 studies are currently being planned. [13]

Quality of life will also be assessed in this study. If results are favourable a larger randomized phase 3 study with emphasis on the effects of treatment on quality of life will be planned.

It would not be possible to perform his study as part of a retrospective audit as Cetuximab is not currently funded in the .N.H.S. for patients who are eligible to receive platinum based chemotherapy Therefore patients who receive Cetuximab and radiotherapy as standard therapy have co-morbidity which may bias the result of any cost analysis. To eliminate bias we plan to randomise into two identical populations

<u>1.1c Accelerated Radiotherapy</u>

Cetuximab can be safely given with accelerated radiotherapy regimes without increasing late toxicity [1]. Accelerated radiotherapy been shown to improve survival when compared to conventional 5 fraction a week radiotherapy [10]. This is not necessarily the case with cisplatin based accelerated chemoirradiation where late toxic effects especially with regard to swallowing dysfunction are common [11, 12]. This may further improve the therapeutic ratio but is a subject for further studies

However accelerated or hyperfractionated radiotherapy is not available as a standard therapy in our unit due to capacity issues. We may treat selected patients using the DAHANCA regime, treating patients with 6 fractions per week however locally this is restricted to

patients with node negative stage 2 or 3 squamous cell carcinoma of the larynx or hypopharynx (i.e. T2/3 N0). Patients treated with accelerated radiotherapy are excluded from the study as we wish the study treatment fractionation schedules to be uniform. The decision whether to treat these patients with accelerated radiotherapy or chemoradiotherapy is a decision made by the clinician taking in to account individual patient factors and tumour bulk.

1.1d Neoadjuvant Chemotherapy

Taxotere, Cisplatin and 5FU (T.P.F.)chemotherapy followed by chemoradiotherapy has been shown to improve survival in selected patients with squamous cell carcinoma of the head and neck.[15,16] This treatment is not currently funded in our network but may be available in Spring/Summer 2008 following approval of the local development plan by the primary care trust cancer commissioners. Neoadjuvant chemotherapy is an exclusion prior to participation in this study, patients fulfilling the local criteria for neoadjuvant therapy with TPF i.e. will not be recruited to the study. [15]
Patient who have received neoadjuvant cisplatin and 5FU based chemotherapy alone will also be excluded from the study. Locally this is a limited population of patient (patients with carcinoma of larynx or hypopharynx being selected for an organ sparing approach who would otherwise undergo laryngectomy) and this is not thought to be a barrier to recruitment.

Homogeneity of population in both arms of the study is required. If patients receiving neoadjuvant chemotherapy were not excluded from the study an in balance could occur given the numbers of patients involved

In our unit only patient fulfilling the entry criteria for the study by Posner et al [15] are considered for neoadjuvant therapy with triplet therapy (T.P.F.). (treatment request made by individual funding request to Primary Care Trust) While a small survival benefit was seen in the study by Vermorken et al in this study a high proportion of patients suffered breaks in treatment or did not complete treatment. In this study patients received radiotherapy alone rather than chemoradiotherapy which has subsequently been shown to be superior therapy. The addition of Taxotere for the less fit population of patients in the Vermorken study may be simply making up for sub optimum definitive therapy.

1.1e Benefits of the study

If the total management costs of treating a patient with cetuximab and radiotherapy are not significantly greater than those for cisplatin based chemoirradiation then patients will benefit though having greater access to Cetuximab plus radiotherapy which is not associated with the increased late radiation side effect profile that are associated with cisplatin based chemoirradiation. Cetuximab plus radiotherapy may be the treatment choice for radical treatment in the elderly however the increased drug costs which do not take in to account management of treatment toxicity are a bar to adoption of this treatment in the current NHS climate. This study wishes to investigate whether the lower toxicity profile of this treatment actually represents a cost saving to the NHS as well a potential clinical benefit to patients in terms of quality of life.

1.2 Cetuximab

A novel targeted therapy; cetuximab (ERBITUX®) has recently been introduced in the United States, European Union, Switzerland, Mexico and Argentina, and is also approved in many other countries. Cetuximab is a targeted therapeutic agent, a chimeric IgG1 monoclonal antibody that specifically binds to the EGFR with high affinity, internalising the receptor and preventing the ligands EGF and TGF-α from interacting with the receptors and thus effectively blocking ligand-induced EGFR phosphorylation. In addition, cetuximab has been found to potentiate the effects of chemotherapy and radiotherapy in experimental systems. The dose of cetuximab (initial dose 400 mg/m2 and subsequent weekly doses of 250 mg/m2) has been found to be generally safe and effective in several studies in major tumour types expressing the EGFR. These included colorectal cancer, squamous cell carcinoma of the head and neck and non-small cell lung cancer, with cetuximab given either in combination studies with chemotherapy and radiotherapy or as monotherapy. The main side effects of cetuximab monotherapy are hypersensitivity- and acne-like skin reactions.[13]

1.3 Epidermal growth factor receptor

The EGFR is a transmembrane glycoprotein, which is commonly expressed, in many normal human tissues. It was one of several growth factors and their receptors, which were found to be encoded by proto-oncogenes. It is a member of the tyrosine kinase family of growth factor receptors, and is over-expressed in many human tumour types. The EGFR, when situated in the transmembrane position, has an extracellular domain, which provides a ligand-binding site for epidermal growth factor (EGF) and transforming growth factor alpha (TGFα). The intracellular domain of EGFR is activated upon ligand binding, which triggers the EGF-mediated tyrosine kinase signal transduction pathway and cascades many cellular operations concerning cell growth and division.

Analyses performed in vitro, using cell lines with a high degree of EGFR expression have shown a proliferation of cells in culture, probably due to activation via an autocrine pathway. In contrast, EGFR antagonists, which block the ligand-binding site, have been developed in order to inhibit proliferation of EGFR-expressing cells.

Table 1 indicates the prevalence of EGFR expression in some common tumour types.

Table 1: Prevalence of EGFR expression in common tumour types.

Tumour Type	Percentage of EGFR Expression
Esophagus carcinoma	92%
Squamous cell carcinoma of the head and neck (SCCHN)	90%
Pancreatic carcinoma	89%
Colorectal carcinoma (CRC)	82%
Prostate carcinoma	65%
Bladder carcinoma	65%
Epithelial ovarian carcinoma	60%
Cervical carcinoma	60%
Renal cell carcinoma	50%
Non-small cell lung carcinoma (NSCLC)	50%

1.4 Cetuximab general safety information

From a database of 2315 patients treated in clinical trials with cetuximab alone, in combination with chemotherapy or radiotherapy, a total of 99.2% of patients reported adverse events. 70.3% of patients reported at least one grade 3 or 4 event. Cetuximab-related adverse events were reported for 93.1%% of patients.

The most common side effect of cetuximab is an acne-form rash (grade ≥ 1 76.2%, grade 3/4 11.1%), which usually occurs within the first 3 weeks of treatment and generally resolves without sequelae over time following cessation of therapy. Other side effects (all grades ≥1, grade 3/4) include fatigue/malaise/lethargy (30.1%, 4.2%), nausea/vomiting (24.0%, 2.2%), mucositis/stomatitis (17.5%, 2.3%), infusion related symptoms (15.6%, 2.7%), diarrhea (15.1%, 2.4%), and nail disorders (10.8%, 0.3%). Hypersensitivity reactions have been recorded in about 5.3% (2.4% grade 3/4) of patients. Haematological adverse events are unusual and include anaemia (4.7%, 1.2%) and leukopenia (6.1%, 3.7%).[14]

2. Aims of the study

The aim of the study is to determine the resource effectiveness of Erbitux given concomitantly with radiotherapy when compared cisplatin given concomitantly with radiotherapy within a clinical oncology unit within the U.K.

2..1 Primary Objective

To compare the direct costs of ERT versus CRT taking in to account drug costs, clinical management and the costs of managing treatment related toxicity.

The primary outcome measure of the study is mean overall cost (in pounds sterling) of total therapy from randomization to the end of the late phase of the study follow up in both arms of the study.

2.2 Secondary Objective

To document unplanned gaps in both radiotherapy and chemotherapy treatment delivery in both treatment arms

To document inpatient hospital admission rates in both treatment arms

To assess impact of treatment of Quality of Life

To assess median overall cost (in pounds sterling) of total therapy from randomization to the end of the late phase of the study follow up in both arms of the study.

3. Materials and Methods

20 (10 per study arm) patients with stage 3/4 squamous cell carcinoma of the head and neck who are eligible for radical cisplatin based chemoirradiation would be randomised to receive either cisplatin or Erbitux concomitantly during a standard course of radiotherapy (70GY in 35 fractions), following local protocols regarding PEG insertion and standard monitoring during radiotherapy at New Cross Hospital, Wolverhampton. The study groups will be compared with regard total planned and unplanned consultation time with medical and paramedical personnel, total administered drug costs (excluding pre-diagnosis medications) during the study period, total treatment delivery time and inpatient admission time. Unplanned gaps in radiotherapy and chemotherapy will be documented.

Data regarding investigations undergone during the study period will be obtained from the PACS and local hospital intranet. The patient will routinely have a weekly consultation with medical staff (a routine part of management) when a full drug history for that week will be recorded. Oncology notes and main hospital records will be reviewed and a medical history for that week will be obtained from the patient. Specialist registrars attached to Dr Brammer have one session a week for research and audit as part of their routine timetable and data will be collected by the specialist registrar under the close supervision of Dr Brammer.

Prior to commencing the study a time and motion study will be carried out to investigate how much time is spent in pharmacy dispensing and preparing both treatment regimes and how much time is direct nursing time is required in the chemotherapy suite for each regime if no complications or additional interventions are given to the patient over and above simple delivery of the treatment. Nursing staff and paramedical personnel will record the duration and nature of any additional intervention or direct contact over and above simple delivery of the treatment schedule (i.e. advice given) on the form attached to the patient's treatment sheet (Chemotherapy prescription or Radiotherapy prescription). Data collection forms will be collected each week for patients on the study by the specialist registrar working on the study.

It is standard departmental protocol not to routinely offer cisplatin based chemoradiotherapy to patients over the age of 70 to the lack of evidence of a survival benefit for patients in this age group [4] unless there are exceptional circumstances suggesting the patient may benefit from therapy

3a. Quality of Life

The EORTC QLQ 30 and QLQ- H+N35 will be completed by the patient at study entry, on the last day of radiotherapy +/- 24 hours, at 6 weeks following completion of radiotherapy +/- 14 days and at 24 weeks +/- 14 days following completion of radiotherapy.
The patient may complete the QoL questionnaire at their hospital visit or they may take the questionnaire home and send it in to the hospital after completion. If the patient wishes to complete the questionnaire at the hospital visit a quiet private area should be provided to allow then to do so.

3.1Inclusion Criteria

Patients with Squamous Cell Carcinoma of the Oropharynx, Larynx and Hypopharynx suitable for radical primary treatment with chemoradiotherapy in the opinion of treating clinical oncologist

Radiotherapy Schedule prescibed to be 70Gy in 35 fractions 5 fraction per week

TNM Stage 3 or 4 (7^{th} editiion)

Patient considered sutable to recieve cisplatin therapy in the opinion of treating clinical oncologist

Age 18-70

Expected survival greater than 6 months·

Patient able to give informed consent

·Haematological Parameters at study entry: -

·Haematological Parameters at study entry: -

· Blood cell counts:

Absolute neutrophils > 1.5 x 10^{9}/L

Platelets > 100 x10^{9}/L

Haemoglobin > 10 g/dl (may be correcetd by transfusion where appropriate)

· Renal function:

EDTA-based glomelular filtration rate of > 50 mL/min or a cockcroft gault calculated GFR of > 60 mL/min.

· Hepatic functions:

Serum bilirubin within normal limits.

or AST or ALT < 1.5 x ULN with alkaline phosphatase < 2.5 x ULN.

·Patient compliance and geographic proximity allowing for adequate follow-up.

Female patients potentially able to child bear should use an approved contraceptive method (IUD, birth control pills or barrier device) during and for 3 months after the study. All male patients should take adequate contraceptive precautions during and up to 2 months after the study.

3.2 Exclusion Criteria

Palliative Radiotherapy

Accelerated Radiotherapy

Prior Radical Surgery for Primary Squamous Cell Carcinoma of the Head and Neck (neck disection is allowed)

Treatment within the last 4 weeks with any investigational drug.

Presence of distant metastases.

Evidence of uncontrolled infection.

Mental condition rendering the subject unable to understand the nature, scope and possible consequences of the study.

Neoadjuvant chemotherapy for squamous cell carcinoma of the head and neck prior to study entry.

Preexisiting peripheral sensory neuropathy

3.3 Sample Size

20 patients will be randomised on a 1:1 basis after informed consent has been gained.

3.4 Study Duration

Patients will be randomised to the study over an 12-month duration

3.5 Concomitant Cisplatin Chemoradiotherapy Schedule

Cisplatin 40mg/m2 over 2 hours plus1 litre normal saline over 2 hours as pre and post hydration (as per standard local protocol) delivered weekly during radiotherapy, 70Gy in 35 fractions over 47 days. Antiemetics 8mg ondansetron i.v. and 8 mg dexamethasone i.v. Post treatment oral antiemetics as required on an individual patient basis.

PEG insertion as per local protocol.

3.6 Concomitant Erbitux and Radiotherapy Schedule

Erbitux (cetuximab) 400 mg/m2 over 2 hours1 week prior to radiotherapy followed by Cetuximab 250 mg/m2 over 1 hour weekly during radiotherapy, 70Gy in 35 fractions over 47 days. Pre medication prior to Cetuximab of 50mg diphenhydramine and 8mg i.v. dexamethasone.

Cetuximab for the purposes if the study will be provided free of charge from Merck Pharma.

PEG insertion as per local protocol. (see appendix 1)

4. Monitoring during therapy

The acute phase monitoring period will run from randomisation to 6 weeks following the last fraction of radiotherapy. Patients must complete the course of radiotherapy to be included in the final analysis.

All consultations/visits to the hospital will be documented in terms of overall time, therapeutic interventions (including advice given), tests requested and drugs, medicinal devices, dressings and food supplements prescribed. Each week a concomitant drugs log will be fully documented.

All inpatient stays will be documented in terms of overall time, therapeutic interventions (including advice given), tests requested and drugs, medicinal devices, dressings and food supplements prescribed.

The above will be costed in terms of overall financial cost of drugs, dressings, medicinal devices, investigations performed and food supplements prescribed. A further analysis will estimate total nursing time, radiographer time, medical personnel time and Dietitian time

spent with each patient. The overall time spent in the chemotherapy suite per patient will also be documented. Costs will be applied from the UK Department of Health Price Tariff.

Acute and Late Treatment related toxicity requiring treatment will be graded according to the NCIC Common Toxicity Criteria version 3.

The second phase of the monitoring "late phase" will document all investigations and interventions thought to be a consequence of the treatment given from 6 weeks after completion of the final radiotherapy to 24 weeks following the final radiotherapy fraction. On going toxicities will be recorded. All patients are routinely reviewed monthly following radical radiotherapy.

All hospital visits/interventions during the acute phase (start of therapy to 6 weeks following the completion of radiotherapy) will be 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 will be included in the analysis.
If the patient's cancer recurs in the assessment phase, costs associated with tumour recurrence will not be included in the analysis.

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

5. Follow Up Schedule

Day 0 = 7 days prior to commencement of radiotherapy

Weekly during radiotherapy and in the post RT phase until discharged by CNS in head and neck RT toxicity clinic as per local protocol– i.e. review Day 7, 14, 21 etc etc .

6 –8 weeks following completion of radical (chemo)radiotherapy in joint ENT clinic

then monthly for a period of 5 months.

6. Statistical Analysis.

All patients completing 35 fractions of radiotherapy will be included in the analysis

The study group will be comparing costs from the perspective of a third party payer (NHS) using standard methodology developed by the Department of Health and NHS Modernisation Agency. Costs will be assessed in terms of mean, and the range of:

Total drug cost in the acute phase

Total treatment time in the chemotherapy suite

Total investigation costs in the acute phase

Total Planned Treatment Cost

Total Unplanned Treatment Cost

Total Overall Cost in the Acute Phase

Total Medical Personnel time spent with patient in the Acute Phase

Total Dietitian Time spent with patient in the Acute Phase

Total Nursing Time spent with patient in the Acute Phase

Total SALT (Speech and Language Therapist) time spent with patient in the Acute Phase

Total radiographer time spent with the patient in the Acute Phase

Total overall cost in the late phase

Total Medical Personnel time spent with patient in the late Phase

Total Dietitian Time spent with patient in the late Phase

Total Specialist Nursing (ENT) Time spent with patient in the late phase

Total SALT (Speech and Language Therapist) time spent with patient in the

Late Phase.

The EORTC QLQ 30 and QLQ- H+N35 will be completed by the patient at study entry, on the last day of radiotherapy +/- 24 hours, at 6 weeks following completion of radiotherapy +/- 14 days and at 24 weeks +/- 14 days following completion of radiotherapy.

The QoL scores for both groups will be assessed in terms of mean, range and standard error jand difference between the populations will be assessed using the paired t test.

Patients are intensively monitored during radiotherapy as part of standard protocol at New Cross Hospital this ensures that any potential complications are averted before crisis point. We have not need to admit a patient to intensive care as a result of radiotherapy toxicity for head and neck cancer for more than 5 years. If a patient does require Intensive care admission during the study period the patient If a patient did require Intensive care admission during the study period this may affect the mean cost of the treatment for that arm but not the median as the rate of intensive care admission would be expected to be very low.. Any intensive care admissions will be recorded and reported in the final analysis.

7.Dose modifications and treatment alterations

7.1Cetuximab

7.1a Skin toxicities

If a subject experiences a grade 3 skin toxicity (as defined in the US National Cancer Institute's - Common Toxicity Criteria [NCI-CTC] version 3), cetuximab therapy may be delayed for up to two consecutive infusions without changing the dose level. For grade 1 or 2 acne-like rash treatment with topical antibiotics (e.g. benzoylperoxide, erythromycin) or

systemic antibiotics (e.g. oral tetracyclines such as doxycycline 100 mg od) should be considered. Patients with grade ≥ 3 reactions should be referred to the dermatologist for advice and management. If pruritus occurs an oral antihistamine is advised. In case of dry skin the use of emollient creams is beneficial. Fissures may occur in dry skin and topical dressings are helpful. If the toxicity resolves to grade 2 or less by the following treatment period, treatment may resume. With the second and third occurrences of grade 3 skin toxicity, cetuximab therapy may again be delayed for up to two consecutive weeks with concomitant dose reductions to 200 mg/m^2 and 150 mg/m^2, respectively. Cetuximab dose reductions are permanent. Subjects should discontinue cetuximab if more than two consecutive infusions are withheld or a fourth occurrence of a grade 3 skin toxicity occurs despite appropriate dose reduction see figure 1.

However, if in the opinion of the investigator the discontinuation of cetuximab is considered necessary, the subject should be withdrawn immediately.

The dose of cetuximab will be adjusted for cetuximab-related grade 3 skin toxicities only.

7.1b Allergic/hypersensitivity reactions

In each case of allergic/hypersensitivity reaction, the investigator should implement treatment measures according to the best available medical practice. Based on previous experience with cetuximab allergic/hypersensitivity reactions, the treatment guidelines as described in table 2 may be applicable.

Re-treatment following allergic/hypersensitivity reactions:

Once a cetuximab infusion rate has been decreased due to an allergic/hypersensitivity reaction, it will remain decreased for all subsequent infusions. If the subject has a second allergic/hypersensitivity reaction with the slower infusion rate, the infusion should be stopped, and the subject should be removed from the study. If a subject experiences a Grade 3 or 4-allergic/hypersensitivity reactions at any time, cetuximab should be discontinued.

7.1c Other reasons for cetuximab discontinuation

If a subject develops an intercurrent illness (i.e., infection) that, in the opinion of the investigator mandates interruption of cetuximab therapy, that intercurrent illness must resolve within a time frame such that no more than two consecutive infusions are withheld. After the interruption of treatment, the subject will continue with a cetuximab dose of 250 mg/m^2 at subsequent visits or the last dose before the interruption if there have been previous dose reductions.

If therapy must be withheld for a longer period of time, the subject will be removed from the study treatment. In special cases, the investigator may request that the patient continues to receive cetuximab (the investigator must ask permission from the Investigator-Sponsor).

figure 1 Treatment adjustment in the event of grade 3 skin toxicity considered to be related to cetuximab.

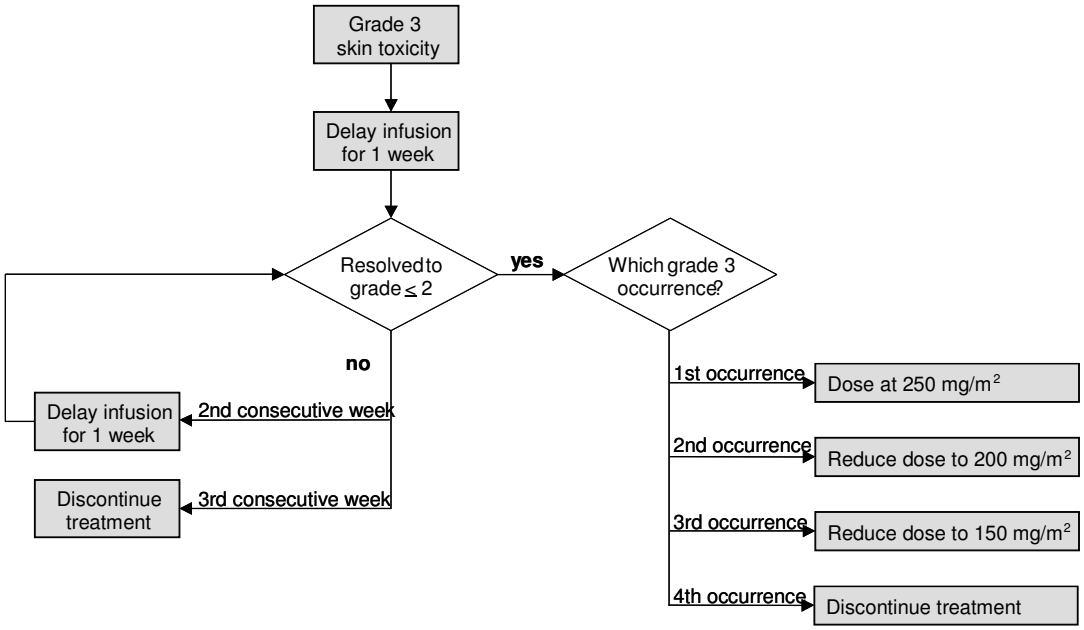

Table 2 :Treatment adjustment in the event of cetuximab caused allergic/hypersensitivity reaction.

CTC Grade Allergic/ Hypersensitivity Reaction	Treatment
Grade 1	Decrease the cetuximab infusion rate by 50% and monitor closely for any worsening. The total infusion time for cetuximab should not exceed 4 hours.
Grade 2	Stop cetuximab infusion. Administer bronchodilators, oxygen, etc. as medically indicated. Resume infusion at 50% of previous rate once allergic/hypersensitivity reaction has resolved or decreased to Grade 1 in severity, and monitor closely for any worsening
Grade 3 or Grade 4	Stop the cetuximab infusion immediately and disconnect infusion tubing from the subject. Administer epinephrine, broncho- dilators, antihistamines, glucocorticoids, intravenous fluids, vasopressor agents, oxygen, etc., as medically indicated. Subjects must be withdrawn immediately from the treatment and must not receive any further cetuximab treatment.

7.2 Cisplatin

7.2a Haematological Toxicity

Suspend further cisplatin administration until platelet count greater than 100 x 10^9

Suspend further cisplatin administration until neutrophil count greater than 1.5 x 10^9

7.2b Renal Toxicity

Grade 1 toxicity suspend further cisplatin administration until recovery

Grade 2 toxicity stop chemotherapy continue treatment with radiotherapy alone

8. Randomisation

Patients will be randomised on a1:1 basis. 20 sealed envelopes will be held by the R+D department at New Cross Hospital each will contain a card with either Cisplatin or Erbitux written on it. An envelope will be selected by an individual independent from the study for each individual patient. (Note this study will not involve any direct patient contact from New Cross R+D directorate research nurse staff, the only direct involvement of the R+D staff will be the process of randomisation)

9. Instructions for the Preparation and Administration of CETUXIMAB 5 mg/mL

9.1 Dosage and Administration Procedure:

Initial dose:

The total initial dose (first infusion) and rate of infusion are described in section 3.5. Patients must be pre-treated with an antihistamine and a steroid. Observe the patient during infusion and for one hour afterwards. Check the vital signs pre-, mid-, post- and one hour post-infusion. Use a sterile 0.9% NaCl solution to flush the line at the end of infusion.

Further infusions

The dose for further infusions and rate of infusion are described insection 3.5. It is recommended that the patient is pre-treated with an antihistamine prior to each infusion. Observe the patient during infusion and for one hour afterwards. Check the vital signs pre-, mid-, post- and one hour post-infusion. Use a sterile 0.9% NaCl solution to flush the line at the end of infusion.

Do not mix cetuximab with any intravenously administered medicinal product other than a sterile 0.9 % NaCl solution. Use a separate infusion line for cetuximab infusion. For dose reduction due to adverse events, see section 7.1

9.2 Preparation and Administration of the Infusion

Cetuximab solution contains no antimicrobial preservative or bacteriostatic agent. This means care must be taken to ensure aseptic handling when preparing the infusion. There are two options:

Syringe Pump:

Calculate the required amount of cetuximab per patient and administration (e.g., 250 mg/m² for a 2 m² patient = 500 mg cetuximab). Calculate the required amount in volume cetuximab solution at 5 mg/mL (e.g., 500 mg cetuximab = 100 mL cetuximab 5 mg/mL)

Draw up the volume calculated above from one or several cetuximab 5 mg/mL vials, using one or several appropriate sterile syringes attached to a suitable needle.

Remove the needle, affix the infusion line to the first filled syringe, and prime it with cetuximab.

Put the first filled syringe into the syringe pump and set the rate. Repeat for remaining syringes.

Monitor the infusion rate. The calculated infusion rate must not exceed the maximum infusion rate of 10 mg/min, i.e. 120 mL/h of the ready-to-use solution.

Use a sterile 0.9% NaCl solution to flush the line at the end of infusion.

Infusion Pump or Gravity Drip:

Calculate the required amount of cetuximab per patient and administration (e.g., 250 mg/m² for a 2 m² patient = 500 mg cetuximab). Calculate the required amount in volume cetuximab solution at 5 mg/mL (e.g., 500 mg cetuximab = 100 mL cetuximab 5 mg/mL)

Take an infusion bag of adequate size (e.g., 250 mL) of 0.9% NaCl solution for infusion (isotonic saline for infusion).

Draw up the volume calculated above from the NaCl bag, using an appropriate sterile syringe attached to a suitable needle. Discard the drawn up NaCl solution.

Draw up the volume calculated above from one or several cetuximab 5 mg/mL vials, using one or several appropriate sterile syringes attached to a suitable needle.

Fill the calculated volume of cetuximab into the NaCl infusion bag.

Affix the infusion line and prime it with cetuximab before starting the infusion.

Monitor the infusion rate. The calculated infusion rate must not exceed the maximum infusion rate of 10 mg/min.

Use a sterile 0.9% NaCl solution to flush the line at the end of infusion.

A one-hour observation period is recommended after the cetuximab infusion.

For the initial dose, the recommended infusion period is 120 minutes. For subsequent weekly doses, the recommended infusion period is 60 minutes.

The maximum infusion rate must not exceed 10 mg/min (i.e., 2 mL/min of the 5 mg/mL solution, or, after dilution of 1 part cetuximab 5 mg/mL in 4 parts 0.9%-NaCl solution (1:5 dilution) 10 mL/min = 600 mL/h).

9.3 Recommended materials, compatibility and stability

Infusion sets or syringes made of polyethylene, polyurethane, polyolefine thermoplastic, polyamide glass microfibre, polypropylene and polyvinyl chloride have been tested for compatibility with cetuximab, and are recommended for use.

Cetuximab is stable, and is compatible with infusion systems made from any combination of the recommended infusion system components when administered at room temperature (up to 25°C). Preparations of cetuximab in the recommended infusion containers are chemically and physically stable for up to 48 hours at controlled room temperatures up to 25 °C. The product contains no antimicrobial agent and should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. In-use storage at 2-8 °C should not exceed 24 hours, unless preparation has taken place under controlled and validated aseptic conditions. Discard any unused portion of the vial.

9.4 Composition of cetuximab

The final product used in this study is a sterile liquid formulation intended for intravenous infusion. It is either manufactured at Boehringer Ingelheim or Merck, and is presented at a concentration of 5 mg/mL in type 1 glass vials closed with a Flurotec-coated rubber stopper. Both of the primary packaging materials are of Ph. Eur. quality. It is presented as a dosage form of 50 mg/10 mL, 250 mg/50 mL and 500 mg/100 mL in vials of nominal volume of 10 mL, 50 mL and 100 mL respectively.

The composition of the formulated drug product and the respective functions and quality standards of the various ingredients are presented below. Please note that these are nominal values.

Composition of cetuximab drug product (New Formulation)

Component	Amount	Amount (mg/mL)	Function	Quality standards
Cetuximab, chimeric antibody	5 mg/mL	5 mg/mL	Active ingredient	In-house specification
Sodium chloride	100 mM	5.844 mg/mL	Isotonicity	Ph. Eur.

			agent	
Glycine	100 mM	7.507 mg/mL	Stabilizer	Ph. Eur.
Polysorbate 80 VS	0.01% (w/v)	0.100 mg/mL	Stabilizer	Ph. Eur.
Citric acid monohydrate	10 mM	2.101 mg/mL	Buffer	Ph. Eur.
Sodium Hydroxide 1M	q.s. to pH 5.5	q.s. to pH 5.5	For pH adjustment	Ph. Eur.
Water for injection	ad 1 mL	ad 1 mL *	Diluent	Ph. Eur.

* Filled into 10, 50 or 100 mL vials. The solution is overfilled for each of the planned presentations to assure the specified extractable volume. This does not represent a risk for the patient because the dose to be administered is calculated and controlled for each individual patient.

10. Adverse Event Reporting

10.1 Definition of adverse event, adverse drug reaction and serious adverse event

Adverse events (or adverse experience) (AE):

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Due to regulatory requirements, events occurring during pre- and post-treatment periods should also be designated as AEs. Therefore, safety surveillance - reporting of (S)AEs - commences at the time when the subject is enrolled into the study (date of signature of the informed consent) until the End of Study Visit has been performed. Therefore events occurring in the period between the signed informed consent and beginning of the study drug administration are to be designated as AEs. This procedure complies with requirements by some authorities.

Adverse drug reaction (ADR):

All noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions (ADRs).

The phrase “responses to a medicinal product” means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility i.e. the relationship cannot be ruled out.

Serious adverse event or reaction/experience (SAE):

A serious AE (experience) or reaction is any untoward medical occurrence that at any dose:

Results in death

Is life-threatening

NOTE: The term ”life-threatening” in the definition of ”serious” refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Requires in-patient hospitalization or prolongation of existing hospitalization

Results in persistent or significant disability/incapacity

Is a congenital anomaly/birth defect or

Is an important medical event

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in cases of important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room, or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse, or malignant tumours when they are histologically different from the primary tumour.

Other events to be treated as SAEs

<u>Exposure to drug during pregnancy/lactation.</u>

In principle, pregnancy and the lactation period are exclusion criteria. In the event of a pregnancy occurring during the course of a study, the subject must be withdrawn from study drug immediately. The Investigator-Sponsor must be notified without delay and the subject followed during the entire course of the pregnancy and postpartum period. Parental and neonatal outcomes must be recorded even if they are completely normal and without AEs. The “Serious Adverse Event Form” (SAE report form) should be used, even though pregnancy is not considered a SAE. No “serious criterion box” should be checked. The SAE report form is solely used to ensure expedited reporting.

<u>Events not to be treated as SAEs</u>

Progression of disease is not to be regarded as a SAE.

Due to the seriousness of the disease in this study, certain conditions defined as SAEs will be excluded from expedited reporting on a SAE report form:

Elective hospitalization and surgery for treatment of disease

Elective hospitalization to simplify treatment or study procedures

Methods of recording and assessing adverse events

All AEs must be documented in the appropriate section of the CRF. For SAEs, a SAE report form (initial or follow up) must be completed in addition.

The following aspects must be recorded for each event in the CRF:

A description of the AE in medical terms, not as reported by the subject;

The date of onset (start date)

The time of onset in case event started at the day of cetuximab administration (start time)

The date of recovery (stop date)

The time of recovery in case event stopped at the day of cetuximab administration (stop time)

The grade as assessed by the investigator according to the definitions in NCI-CTC, Version 3

Grade 1 = mild

Grade 2 = moderate

Grade 3 = severe

Grade 4 = life-threatening or disabling

Grade 5 = death related to AE

The causal relationship to cetuximab or chemotherapy as assessed by the investigator; the decisive factor in the documentation is the temporal relation between the AE and the study drug. The following judgments of the causality to study drug or study procedures are to be used:

Not Related = There is not a temporal relationship to study drug administration (too early, too late, or study drug not taken), or there is a reasonable causal relationship between another drug, concurrent disease, or circumstance and the AE.

Not Likely = There is a temporal relationship to study drug administration, but there is not a reasonable causal relationship between the study drug and the AE,

Possible = There is a reasonable causal relationship between the study drug and the AE. Dechallenge information (information referring to withdrawal of drug) is lacking or unclear.

Probable = There is a reasonable causal relationship between the study drug and the AE. The event responds to dechallenge (withdrawal of study drug). Rechallenge is not required.

Certain/Definite = There is a reasonable causal relationship between the study drug and the AE. The event responds to dechallenge and recurs with rechallenge, when clinically feasible.

Action taken on cetuximab (none, medication discontinued, dose reduction, medication delayed, reduction of infusion rate).

Other action (none, concomitant medication given, new or prolonged hospitalization, procedural surgery, chemotherapy delayed, chemotherapy discontinued, chemotherapy dose reduction).

The outcome according to the following definitions:

Recovered with sequelae.

Recovered without sequelae.

Ongoing, no therapy.

Ongoing, therapy.

Died.

Change in toxicity grade/severity.

Seriousness: yes or no

In case of SAEs it must be indicated whether the SAE is the leading event, i.e. the primary medical reason for SAE reporting.

If in any one subject the same AE occurs on several occasions, then the AE in question must be documented and assessed anew each time.

10.2 Procedure for reporting serious adverse events

In the event of the occurrence of any clinical AE or abnormal laboratory test value that is serious or medically important during the course of the study or the post-treatment period, irrespective of the treatment received by the subject, the investigator is obliged to immediately inform the Investigator-Sponsor.

The immediate report by the investigator to the Investigator-Sponsor shall be followed by detailed, written reports using the SAE report form (for an “initial” SAE or for “follow-up” information on a previous SAE). The immediate and follow up reports shall identify subjects by unique code numbers assigned to the latter.

For names, addresses, telephone and fax numbers, see SAE report form.

The Investigator-Sponsor shall ensure that all reporting requirements according to the respective national law are followed. “Expectedness” to be assessed with regard to the valid IB for cetuximab. “Expectedness” with respect to a comparator or a concomitant anti-cancer treatment, if applicable, is to be assessed according to either the respective IB or versus the

Product Information. A CIOMS-1 format shall be used for submitting expedited reports to the competent authorities, the ethics committee and to all investigators involved in this study according to all appropriate national and international laws. Where necessary, the CIOMS-1 form shall be accompanied by the relevant pages of the case report form.

Cetuximab SUSARs represent Serious Adverse Events related to cetuximab (=Adverse Reactions), considered "unexpected" with regard to the valid IB for cetuximab.

With respect to cetuximab, the Investigator-Sponsor shall only copy Merck in any cetuximab individual case safety report, which has been submitted expeditedly to the competent authorities. The report to Merck shall be sent via Fax only at the same time of reporting to the competent authorities.

The Investigator-Sponsor shall ensure that for a reported death of a subject, the investigator shall supply the Investigator-Sponsor and the Ethics Committee with any additional information as requested.

10.3 Monitoring of subjects with adverse events

Any AE that occurs in the course of a clinical study must be monitored and followed up until the End of Study Visit. In addition SAEs must be reported via a SAE report form

It is the responsibility of the investigator that any necessary additional therapeutic measures and follow-up procedures are performed.

10.4 Overdose and intoxication with Cetuximab

There is no experience with single doses of cetuximab higher than 500 mg/m² body surface area in human clinical trials. In the event of a drug overdose occurring in the course of the present study, this must be reported as a SAE.

10.5 Clinically relevant adverse events related to cetuximab

Skin reactions are the most common AEs associated with cetuximab. They usually presents as an acneform rash, acne-like rash or, less frequently, as nail disorders. Acneform rash/Acne-like rash usually occurs in the first 3 weeks of treatment on the face, upper chest and back, but occasionally extends to the extremities. It occurs as multiple follicular or pustular lesions characterized histologically as lymphocytic perifolliculitis or suppurative superficial folliculitis. It tends to resolve without sequelae over time following cessation of therapy. In patients who have received cetuximab in doses lower than 100 mg/m^2, the acne-like rash has been reported infrequently and has been restricted to grades 1 and 2. The etiology of the acne-like rash is believed to be the result of cetuximab interfering with the role of EGFR in the homeostasis of epidermis, hair follicle and sebaceous glands as well as in the regulation of cutaneous inflammation. Clinical trials in patients with CRC have shown that the occurrence of acne-like skin reactions were correlated with better efficacy outcomes (response, and time to progressive disease and survival).

Nail disorders: Another typical but less frequent reported AE is nail disorder which presents as pain, tenderness and fissuring of the distal finger tufts to different degrees. The patients developed paronychial inflammation with associated swelling of the lateral nail folds of the

toes and fingers. The most commonly affected digits are the great toes and thumbs. From investigator reports, it is known that nail disorders may persist for up to 3 months after discontinuation of cetuximab. Dermatological advice should be sought.

Allergic/hypersensitivity reactions: Grade 3 or 4 hypersensitivity reactions (including allergic and anaphylactic reactions) characterized by the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension, have been observed in 2.5% patients treated with cetuximab. Approximately 80% of all allergic/hypersensitivity reactions occurred during the first infusion of cetuximab and were observed during or within 1 hour of the completion of the infusion.

Prior to the first administration of cetuximab, patients must be premedicated with an antihistamine and a steroid. This premedication is also recommended prior to all subsequent infusions of cetuximab as there were patients who experienced their first severe allergic/hypersensitivity reaction during later infusions. In studies with cetuximab to date, patients who experienced severe reactions received standard treatment, and all with the exception of three patients recovered without sequelae and were withdrawn from the studies concerned. Three reports exist which are associated with death.

The occurrence of allergic/hypersensitivity reactions does not appear to be related to single-drug therapy or combination therapy, underlying disease, or previous exposure to murine monoclonal antibodies. Mild to moderate allergic/hypersensitivity reactions can generally be managed by slowing the infusion rate of cetuximab

11.Special precautions

11.1Cetuximab administration

Allergic/Hypersensitivity reactions

Allergic/Hypersensitivity reactions may occur during or following the administration of cetuximab. Subjects must therefore be pretreated with an appropriate antihistamine before the first infusion. Pretreatment with an antihistamine is recommended before subsequent infusions. As a routine precaution, subjects enrolled into this study should be observed closely for any potential AEs and a physician able to give emergency medical treatment must be present from the start of cetuximab infusion until at least 1 hour after the end of the infusion. The subject should be observed in an area with resuscitation equipment and other agents available (epinephrine, prednisolone equivalents etc). Should an allergic/hypersensitivity or infusion reaction to cetuximab occur, then the subject must be treated according to the best available medical practices. For adjustment of cetuximab treatment, see section 7.1 Dose modifications and treatment alterations for cetuximab. Grade 3 or 4 allergic/hypersensitivity reactions require immediate interruption of the cetuximab infusion, appropriate medical measures and permanent discontinuation of treatment. Subjects should be carefully monitored until the complete resolution of all signs and symptoms.

Skin reactions

The most common AE associated with cetuximab administration are skin reactions, particularly acne-like rash. If a subject experience a grade 3 skin reaction, cetuximab therapy must be interrupted for up to 2 consecutive weeks. Treatment may only be resumed, if the reaction has resolved to grade 2. For recommended adjustments in dose regimen, see section 7.1 Dose modifications and treatment alterations for cetuximab. If grade 3 skin reactions occur a fourth time or do not resolve to grade ≤ 2 during treatment interruption, permanent discontinuation of cetuximab treatment is required.

Interstitial pneumonitis

Severe interstitial pneumonitis has been described in subjects treated with the EGFR-pathway targeting therapy gefitinib. To date, no increased risk of interstitial pneumonitis has been identified with cetuximab. Nevertheless, all subjects must have adequate chest imaging prior to commencing cetuximab therapy in the study, as a safety precaution in order to document the baseline pulmonary condition. If there are respiratory symptoms at study entry, lung function tests and further diagnostic procedures must also be undertaken in order to diagnose pre-existing pulmonary fibrosis or interstitial pneumonitis. Furthermore, subjects will be regularly questioned about pulmonary symptoms during the study. Should pulmonary symptoms appear or worsen during or after cetuximab treatment, a detailed description is required and investigators should use their discretion in ordering such diagnostic procedures as are necessary to elicit an accurate diagnosis.

11.2 Chemotherapy administration

Cisplatin is a commercially available antineoplastic agent(s). Investigators should use the approved package inserts of these drugs for complete prescribing information, including any special precautions.

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17. Appendix 1

Local Protocol re PEG feeding tube insertion

The indications for PEG insertion prior to RT

patients receiving chemoradiotherapy

patients relieving accelerated radiotherapy (see trial exclusion criteria)

significant weight loss or dysphagia prior to radiotherapy

oral cavity irradiation (except unilateral oral cavity irradiation)

large irradiated volume i.e. nasopharynx

Appendix 2

Local Protocol re Routine investigations during radiotherapy treatment for head and neck cancer

Weekly FBC for patients undergoing radiotherapy. Blood transfusion is required if Haemoglobin levels drop below 11g/dl

Weekly F.B.C. and U+E for patients receiving cisplatin based chemotherapy. To be taken 24 hr prior to drug therapy.

Appendix 3

Local Protocol re Routine Management Plan for Patients Under Going Radiotherapy for Head and Neck Cancer

All patients to have thermoplastic immobilisation shell for RT.

Radiotherapy to be C.T. planned. GTV, primary PTV and secondary PTV (lymph node groups at risk) to be delineated on CT plan.

All patients to have dental and dietetics assessment pre radiotherapy

All patients reaching the criteria for PEG tube insertion to have PEG tube inserted prior to radiotherapy (if contra indicated for NG tube insertion during radiotherapy or surgical jejunostomy placement prior to RT)

All patients to be reviewed weekly during radiotherapy by Oncologist.

All acute toxicities to be graded according to CTC version 3 criteria and recorded by oncologist each week during radiotherapy

All patients to be reviewed weekly post radiotherapy in ENT clinical nurse specialist led RT toxicity clinic until acute radiotherapy side effects are settling. (grade 2 or less).

All acute toxicities to be graded according to CTC version 3 criteria and recorded by ENT clinical nurse specialist weekly until discharge from toxicity clinic

All patients to be reviewed in the Joint ENT/Oncology clinic 6-8 weeks following radiotherapy for assessment of response

Appendix 4

NCI Common Toxicity Grading Criteria

Grade 5 = death due to toxicity

Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
WCC	>4	3.0-3.9	2.0-2.9	1.0-1.9	<1
Plats	Normal	75-Normal	50-75	25-50	<25
Hb	Normal	10-Normal	8-10	6.5-7.9	<6.5
Granulocytes	>2	1.5-1.9	1.0-1.4	0.5-0.9	<0.5
Lymphocytes	>2	1.5-1.9	1.0-1.4	0.5-0.9	<0.5
Haemorrhage	none	mild, no transfusion	gross 1-2 units transfusion/ episode	gross 3-4 units transfusion/ episode	massive >4 units transfusion/ episode
Infection	none	mild	moderate	severe	life threatening
Nausea	none	mild, able to eat reasonable intake	intake significantly reduced	no significant intake	
Vomiting	none	1 episode /24hs	2-5 episodes /24hs	6-10 episodes /24hs	>10episodes/ 24s or requiring parenteral support
Diarrhoea	none	increase of 2-3 stools per day over pre Tx	increase of 4-6 stools per day nocturnal stool or moderate cramping	increase of 7-9 stools per day, incontinence or severe cramping	increase of >10 stools per day, grossly bloody stool or parenteral support
Stomatitis	none	painless ulcer or mild soreness	painful erythema, oedema or ulcers but can eat	painful erythema oedema or ulcers and cannot eat	requires parenteral or enteral support
Bilirubin	Normal		<1.5 x N	1.5-3.0 x N	>3.0 x N
Transaminase	Normal	<2.5 x N	2.5-5 x N	5 - 20 x N	>20 x N
Alk Phos	Normal	<2.5 x N	2.5-5 x N	5 - 20 x N	>20 x N
Liver-Clinical	no change			pre coma	coma
Creatinine	Normal	<1.5 x N	1.5-3.0 x N	3.1-6 x N	>6 x N
Proteinuria	no change	1+ or <0.3g% or <3g/l	2-3+ or <0.3-1g% or 3-10g/l	4+ or >1.0g% or <10g/l/l	nephrotic syndrome

Heamaturia	negative	micro only	gross/no clots	gross +clots	requires transfusion
Alopecia	no loss	mild hair loss	pronounced or total hair loss		
Pulmonary	no change	asymptomatic abnormality in pulmonary function tests	dyspnoea on exertion	dyspnoea on normal activity	dyspnoea at rest
Cardiac Arrhythmias	none	asymptomatic	recurrent or persistent, no therapy required	requires treatment	hypotension, ventricular tachycardia or fibrillation
Cardiac Function	none	asymptomatic decline of resting ejection fraction by <20% of base line value	asymptomatic decline of resting ejection fraction by >20% of base line value	mild CHF responsive to therapy	severe or refractory CHF
Cardiac - ischaemia	none	non-specific T wave flattening	asymptomatic ST ot T wave change suggesting ischaemia	angina without evidence of myocardial infarction	acute myocardial infarction
Cardiac - pericardial	none	asymptomatic effusion no therapy required	pericarditis	symptomatic effusion drainage required	tamponade, drainage urgently required
Hypertension	no change	asymptomatic transient increase by greater that 20mmHg or to >150/100 if previously normal-no treatment required	recurrent or persistent increase by greater that 20mmHg or to >150/100 if previously normal-no treatment required	requires therapy	hypertensive crisis
Hypotension	no change	changes requiring no therapy including	requires fluid replacement or other	requires therapy and hospitalisation resolves	requires therapy and hospitalisation for > 48hrs

		transient orthostatic hypotension	therapy but not hospitalisation	within 48hrs of stopping the agent	after stopping the agent
Neurosensory	no change	mild paresthesia loss of deep tendon reflexes	mild or moderate objective sensory loss, moderate paresthesia	severe objective sensory loss or paresthesia that interferes with function	
Neuromotor	no change	patient weakness, no objective findings	mild objective weakness without significant impairment of function	objective weakness with significant impairment of function	paralysis
Neurocortical	none	mild somnolence or agitation	moderate somnolence or agitation	severe somnolence or agitation, confusion, disorientation hallucinations	coma, seizures, toxic psychosis
Neuocerebellar	none	slight un-coordination dysdiadokinesis	intension tremor, dysmetria, nystagmus	locomotor ataxia	cerebellar necrosis
Mood	no change	mild anxiety or depression	moderate anxiety or depression	severe anxiety or depression	suicidal intension
Headache	none	mild	moderate or severe but transient	unrelenting and severe	
Constipation	none	mild	moderate	severe	ileus
Hearing	none	asymptomatic,on audiometry only	tinitus	loss interfering with function correctable with hearing aid	incorrectable deafness
Vision	no change			symptomati	blindness

				c subtotal loss of vision	
Skin	none	asymptomatic scattered rash	scattered rash with pruritis or other symptoms	generalised symptomatic erruption	exfoliative or ulcerative dermatitis
Allergy	none	transient rash, drug fever <38C	urticaria, drug fever =38C, mild bronchospasm	serum sickness bronchospasm requires parental med	anaphylaxis
Fever-absence of infection	none	37.1-38C	38.1-40C	>40C for less than 24hs	>40C for more than 24hs
Wt gain or loss	<5%	5-9.9%	10-19.9%	>20%	
Hyperglycaemia mg/dl	<116	116-175	161-250	251-500	>500 or ketoacidosis
Amylase	normal	1.5 x N	1.5-2.0 x N	2.1-5 x N	5.1 x N
Hypercalcaemia	<10.6	10.6-11.5	11.6-12.5	12.6-13.4	>13.5
Hypocalcaemia mg/dl	>8.4	8.4-7.8	7.7-7.0	6.9-6.1	<6.0
Hypomagnesaemia mg/dl	>1.4	1.4-1.2	1.1-0.9	0.8-0.6	<0.5
Fibrinogen	normal	.99-0.76 X control	0.75-0.5 X control	0.49-0.25 X control	<0.24 X control
Prothrombin Time	normal	1.01-1.25X control	1.26-1.5 X control	1.51-2.0 X control	>2.00X control
Partial Thromboplastin time	normal	1.01-1.66X control	1.67-2.33X control	2.34-3.00 X control	>3.00X control

Appendix 5

Patient information sheet

Cost analysis of cetuximab (Erbitux) plus radiotherapy (ERT) versus concomitant cisplatin plus radiotherapy (CRT) within an NHS Oncology Unit

Sponsor - Royal Wolverhampton Hospital's Trust

You have been asked by Dr Brammer to consider entry in to a study we are carrying out here at New Cross Hospital. Before you decide on taking part in this clinical trial, we would like to explain to you why we consider this research project important and what it involves. Please take time to read the following information carefully and discuss it with friends, relatives and your study doctor if you wish. Ask your study doctor if you do not understand anything or if you would like to have more information. Take your time to decide whether or not you would like to participate in this study.

You will have been told that you have been diagnosed with a cancer affecting your throat which will require treatment with a combination of radiotherapy (X ray treatment) and chemotherapy (drug treatment). The commonly used drug treatment at New Cross Hospital in this situation is a drug called Cisplatin which is given once a week as an outpatient along with fluid therapy before and after the chemotherapy. While this is an effective treatment there is a risk of side effects , chemotherapy may affect how your kidneys work and may put you at risk of developing a serious infection. Swallowing difficulties may also occur which may last for some time following completion of your treatment. There is a new drug, Cetuximab (Erbitux) which is more expensive than cisplatin but appears to be equivalent in terms of treating your cancer (although the two drugs have not been trialed head to head). Studies suggest that Cetuximab may have less side effects than the current standard treatment. As this drugs may have a less side effects it may mean that although this drug is more expensive than cisplatin when considering the cost of the drugs to the national health service, it may be cheaper if the full cost of treatment of all the side effects of treatment are considered. We are performing a small study to test the cost effectiveness of the two treatments.

This is a randomized trial this means that you will be allocated to the treatment by chance. If you wished to participate neither you or Dr Brammer could choose which treatment you would receive as this would be decided randomly to prevent any bias affecting the results. If after being randomised to the study you may withdraw your consent and you would be treated by our departmental standard treatment which is Cisplatin and Radiotherapy

We wish to enter 20 patients in to the study. Ten patients would receive Cetuximab and 10 patients Cisplatin with their radiotherapy. You would receive your radiotherapy treatment in the normal way. After treatment you will be reviewed regularly by our Clinical Nurse Specialists until the side effects of your treatment settle and then monthly in the outpatients clinic by your ENT surgeon and Dr Brammer as is our routine practice.

During your treatment we would take a regular review of what treatments or interventions you had received as a consequence of your radiotherapy.

Participation in the study is entirely voluntary. If you do not wish to participate in the study, this would not affect the standard of your care. We would proceed with our standard treatment of chemotherapy and radiotherapy as is our usual practice.

<u>What is the therapy being tested?</u>

Cetuximab is an antibody. An antibody is a protein produced by the immune system to protect the body from foreign invaders like bacteria. Cetuximab is manufactured by Merck KGaA and is a very pure antibody, which acts against a protein called 'Epidermal Growth Factor Receptor (EGFR)', which is also located on tumour cells. A growth factor is a protein that speeds up the growth of cells upon binding to a receptor on the surface of cells . If a cell grows to quickly it may change into a cancer. The EGFR is frequently found on tumour cells in various types of cancer including head and neck cancer. Cetuximab blocks binding of growth factor and related molecules that bind to the EGFR, and thus slows tumour cell growth. In addition, the cancer cells may be destroyed with the help of cells from your own

immune system. Cetuximab is given a drip into an arm vein. The initial dose (first infusion) is 400 mg/m² (for 2 hours) the week prior to the start of radiotherapy, then 250 mg/m² given for 1 hour each week during radiotherapy. Cetuximab may make the "sun burn reaction that occurs during radiotherapy more intense and may cause a rash that looks like acne.

The treatments expected side effect profiles of the two treatments are described below

Concomitant Cisplatin Plus Radiotherapy (CRT)

Treatment will consist of 35 radiotherapy treatments, one treatment a day, 5 days a week. Each radiotherapy treatment will take 2-3 minutes to deliver and you will be in the radiotherapy room 10-15 minutes. Once a week you will have chemotherapy before your radiotherapy treatment, this will be delivered in the chemotherapy outpatient suite. A drip will be put in to the back of your hand and the treatment will be infused slowly over 6 hours. Side effects of the chemotherapy include nausea and vomiting (you will be given anti sickness medications to prevent this) and anaemia (low blood counts), which may require a blood transfusion to correct. In addition the chemotherapy may cause a reduction of the cells in your blood which fight infections. This means that if you get an infection during your treatment you will need urgent antibiotics to fight the infection for you. It is for this reason that we ask you to take your temperature twice a day during your treatment. We will be taking blood tests every week to help monitor this and also to monitor your kidney function as the chemotherapy may affect this.

During the treatment your mouth and throat will get very sore as a consequence of the treatment and you will have problems swallowing. We will give you pain killers for this and food supplements as needed. If you are allocated this treatment we will place a tube in your stomach called a percutaneous gastrostomy (PEG tube) so you can feed and drink without having to swallow at the end of your treatment when it may be painful for you. This is part of usual treatment for patients having cisplatin based chemoradiotherapy in our unit The soreness of the radiotherapy reaction will continue to develop for 2 weeks after completion of the radiotherapy but should settle by 6 weeks following completion of the treatment. Following treatment it is usually necessary to use the PEG tube for at least 3 moths until your swallow returns to normal. Some patients need to use their PEG tube for longer, If you have swallowing difficulties before your treatment you may be more likely to have swallowing problems after treatment. Your skin may also get sore and may blister.

The radiotherapy may also affect your saliva glands, during radiotherapy your saliva may become thick and sticky, after radiotherapy this will reduce but you may be left with a dry mouth.

Cetuximab (Erbitux) Plus Radiotherapy (ERT)

Treatment will consist of 35 radiotherapy treatments, one treatment a day, 5 days a week. Each radiotherapy treatment will take 2-3 minutes to deliver and you will be in the radiotherapy room 10-15 minutes. Once a week you will have Cetuximab which is an antibody against cancer cells before your radiotherapy treatment, this will be delivered in the chemotherapy outpatient suite. A drip will be put in to the back of your hand and the treatment will be infused slowly over 1 hour.

The most common side effects of cetuximab are skin reactions. They usually present as an acne-like rash within the first 3 weeks of treatment on the face, upper chest and back; sometimes they do also appear on arms and legs. These side effects are usually mild but in a small number of patients mat be severe. You should not sun bathe or use a sun lamp during treatment as this may make side effects worse. Less Your nails may also be affected with

pain, tenderness and cracking of finger and toe nails. Rarely following the infusion of Cetuximab you may develop urticaria (hives) or in a few cases a severe allergic reaction which needs an immediate intervention. To help to prevent an allergic reaction, your study will treat you with an antihistamine. Another rare side effects are conjunctivitis. (sore eyes) or shortness of breath

During the treatment your mouth and throat will get very sore as a consequence of the radiotherapy and you will have problems swallowing. We will give you pain killers for this and food supplements as needed. If you are you are having difficulty swallowing liquids at the end of the treatment we may need to out a fine tube though your nose in to your stomach (an NG tube) to feed you this way for 2-3 weeks until the radiotherapy reaction settles and you are able to swallow. Depending on the area we need to treat we may recommend a tube in your stomach called a percutaneous gastrostomy (PEG tube) to help feed you at the end of treatment instead. The soreness of the radiotherapy reaction will continue to develop for 2 weeks after completion of the radiotherapy but should settle by 6 weeks following completion of the treatment. problems after treatment. During treatment your skin is likely to get sore get sore and is likely to blister. If this occurs we will suspend the drug treatment. You will be given creams and dressings to help with the skin reaction. The skin reaction will begin to settle 2-3 weeks following competition of the radiotherapy.
The radiotherapy may also affect your saliva glands, during radiotherapy your saliva may become thick and sticky, after radiotherapy this will reduce but you may be left with a dry mouth.

Not all patients randomized to receive Cetuximab and radiotherapy will require PEG insertion prior to radiotherapy. The decision to insert a PEG will depend whether your tumour has affected your ability to swallow already or whether we may need to treat areas of your mouth with radiotherapy. Please discuss this with your study doctor.
If you have not had a PEG inserted prior to your treatment and you have unexpected severe swallowing difficulties during your treatment we may either pass a small feeding tube into your nose and down in to your stomach or arrange for a PEG to be inserted during your radiotherapy treatment. If you miss any days of your radiotherapy treatment due to this we will catch up the treatment by either treating you twice on one day (in the morning and late afternoon) or occasionally we may add in a treatment on a Saturday.

Treatment Outlines
Arm A

Radiotherapy	↓↓↓↓↓	↓↓↓↓↓	↓↓↓↓↓	↓↓↓↓↓	↓↓↓↓↓	↓↓↓↓↓	↓↓↓↓↓	
Cisplatin		↓	↓	↓	↓	↓	↓	↓
Peg Placement↓								
Week	0	1	2	3	4	5	6	7

Arm B

Radiotherapy		↓↓↓↓↓	↓↓↓↓↓	↓↓↓↓↓	↓↓↓↓↓	↓↓↓↓↓	↓↓↓↓↓	↓↓↓↓↓
Cetuximab	↓	↓	↓	↓	↓	↓	↓	↓

Peg Placement↓ for some patients only.

Week	0	1	2	3	4	5	6	7

What do I have to do if I take part in the study?

It is important that you inform your consultant of any change in your health or any change in your tablets, We will need to know about any new tablets started by your GP or hospital doctor and also may tablets you have got from the pharmacy or heath food shop. For safety reasons, pregnant woman cannot take part in this study.

All patients taking part in this study must agree to use contraception during the study period. In the unlikely event of a pregnancy occurring while you are on treatment your study doctor may need to discuss the option of termination of pregnancy with you

What are the possible benefits of participating?

There may be no benefits to yourself by participating in this study. Cetuximab and radiotherapy may have a lower side effect profile than Cisplatin and radiotherapy. The treatments appears to be equally effective although these have not yet been trialed head to head. If your treatment works, it may prevent the tumour from growing or may even shrink the tumour or let the tumour disappear and both treatments are believed to be equally effective. Even if you do not benefit personally from this study, the information gained may help in the treatment of other cancer patients in the future.

Freedom of participation

It is up to you to decide whether or not you wish to take part. If you do decide to take part you will be given this information sheet and will be asked to sign a consent form. You will receive a personal copy of the signed consent form. If you decide to participate you are still free to withdraw at any time and without giving any reason. This will not affect the standard of care you receive and your study doctor will inform you about other treatment options. However, if you withdraw from the study, you should undergo a careful examination by your study doctor for safety reasons.

What if new information becomes available?

Sometimes during a research project, new information becomes available about the treatment that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in this study. If you decide to withdraw from the study, we will continue to look after you in the best way we can. If new information comes available during the time that this study is conducted, your research doctor may consider it is

in your best interest to withdraw you from the study. He/she will explain the reasons for this to you and arrange for your care to be continued.

What happens when the research study stops?

If you require any further treatment your study will discuss this with you. It is possible that the study may be terminated prematurely. If this happens, your study doctor will explain the reasons to you.

Will my participation in this study be kept confidential and what about my privacy?

The test results will be recorded anonymously – i.e. without your full name, you will only be identified by your initials, date of birth and a patient number. Correct recording of the data is particularly important for the purpose of research and hence for the improvement of drug safety. In order endure that correct information in recorded, authorized representatives of the Royal Wolverhampton Hospitals Trust who is the legal sponsor of the study as well as regulatory authorities and members of the responsible ethics committee must be allowed to review your hospital record. Your permission is required for this. Also, responsible personnel from the Pharmaceutical Company providing the drug may wish to review the data collected for the study, but no identifiable data will be sent to them. Your permission is required for this also. The persons entrusted with data checking are bound to strict confidentiality and data protection laws. If you wish to participate in this clinical trial, you will be asked to agree to this review of your patient record. Your permission is necessary for participating in the study. If the study results are published, confidentiality of the data will be ensured; particularly your name will not be mentioned.

Your family doctor will be informed on your participation to this study.

Thank you for taking time to read this information sheet. If you require any further information, please contact Dr Brammer via 01902695012.

The sponsor for this study is the Royal Wolverhampton Hospitals Trust

Appendix 6

GP Letter

Dear Dr

Your patient _____ has agreed to participate in cost analysis study of Cetuximab (Erbitux) plus radiotherapy (ERT) versus concomitant cisplatin plus radiotherapy (CRT). 20 patients will be randomized in to this study and will be randomized on a 1:1 basis. Cetuximab is a monoclonal antibody against the epithelial growth factor receptor and like standard chemotherapy with cisplatin can be given concomitantly with radiotherapy as a potentially curative treatment for locally advanced squamous cell carcinoma of the head and neck. You patient has been randomized to receive a weekly infusion of _____ along with their radiotherapy.

Potential side effects of Cetuximab include and acneform skin reaction and potentiation of the radiotherapy skin reaction. Potential side effects of cisplatin based chemotherapy include neutropenia and renal failure.

All patients in the study will receive 6 ½ weeks of radiotherapy, during this treatment xerostomia, mucositis and oesophagitis will develop as a consequence of treatment. Side effects will peak 2 weeks following completion of the radiotherapy.

If you require any further information please contact me at New Cross Hospital on 0902 685201.

Yours sincerely

Caroline Brammer

Appendix 7

Written Consent Form

Cost analysis of cetuximab (Erbitux) plus radiotherapy (ERT) versus concomitant cisplatin plus radiotherapy (CRT) within an NHS Oncology Unit

Protocol Version
Patient Identification Number:
Name of Researcher:

Patient please initial box

1. I confirm that I have read and understood the information sheet version…….. for the above study. ☐
2. I have had the opportunity to ask questions and all my questions have been answered to my satisfaction. ☐
3. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
4. I understand that sections of any of my medical notes may be looked at by responsible individuals from regulatory authorities or the Trust, where it is relevant to my taking part in research. I give permission for these individuals to have access to my records and for the data to be transferred to them. ☐
5. I understand that the data collected for the study may be looked at by responsible individuals from the Pharmaceutical Company who is providing the drug for the trial where it is relevant to my taking part in research. I give permission for these individuals to have access to my study records and for the data to be transferred to them ☐
6. I agree that my GP can be informed of my participation in this study. ☐
7. I agree to take part in the above study. ☐

_____	_____	_____
Name of Patient		Date
_____	_____	_____
Name of Person taking consent		Date

Each individual who signs this document must PERSONALLY date his or her signature.

1 for patient, 1 for researcher, 1 to be kept with hospital notes.

Appendix 8

Data Collection Form (Chemotherapy)

Patient Trial number **Patient Initials**

Table 1

Date Required		Additional intervention If yes describe in table 2 (pto)	
	Chemotherapy Cycle1	Yes	No
	Chemotherapy Cycle2	Yes	No
	Chemotherapy Cycle3	Yes	No
	Chemotherapy Cycle4	Yes	No
	Chemotherapy Cycle5	Yes	No
	Chemotherapy Cycle6	Yes	No
	Chemotherapy Cycle7	Yes	No

Table 2 (additional intervention above simple delivery of chemotherapy)

Date	Initals of Health Care Professional	Grade of Health Care Professional	Time spent with patient (in minutes)	Intervention (advice/examination/prescribed/tests arranged etcetc)	Outcome (home/ admit etc)
				PREADMISSION Visit	

Appendix 9

Data Collection Form (Radiotherapy)

Patient Trial number **Patient Initials**

(additional intervention above simple delivery of radiotherapy)

Date	Initials of Health Care Professional	Grade of Health Care Professional	Time spent with patient (in minutes)	Intervention (advice/examination/prescribed/tests arranged etc.etc)	Outcome (home/ admit etc)
				RT Initiation/confirmation of consent	

Appendix 10

Data Collection Form Acute Phase (Dietetics)

Patient Trial number **Patient Initials**

Date	Initials of Health Care Professional	Routine or unplanned or telephone assessment	Time spent with patient (in minutes)	Intervention (advice /tests arranged etc.etc)	Supplements/ Enteral feed prescribed

Appendix 11

Data Collection Form Acute Phase (SALT)

Patient Trial number **Patient Initials**

Date	Initals of Health Care Professional	Routine or unplanned assessment	Time spent with patient (in minutes)	Intervention (advice /tests arranged etc.etc)

Appendix 12

Data Collection Form Acute Phase (CNS)

Patient Trial number **Patient Initials**

Date	Initals of Health Care Professional	Grade of Health Care Professional	Time spent with patient (in minutes)	Intervention (advice/examination/drugs prescribed/tests arranged etcetc)	Routine or unplanned assessment

Appendix 13

Data Collection Form Late Phase (Dietetics)

Patient Trial number **Patient Initials**

Date	Initals of Health Care Professional	Routine or unplanned assessment or telephone	Time spent with patient (in minutes)	Intervention (advice /tests arranged/peg removal etc.etc)	Supplements/ Enteral feed Prescribed

Appendix 14

Data Collection Form Late Phase (SALT)

Patient Trial number **Patient Initials**

Date	Initials of Health Care Professional	Routine or unplanned assessment or telephone	Time spent with patient (in minutes)	Intervention (advice /tests arranged etc.etc)

Appendix 15

Data Collection Form Late Phase (CNS)

Patient Trial number **Patient Initials**

Date	Initials of Health Care Professional	Grade of Health Care Professional	Time spent with patient (in minutes)	Intervention (advice/examination/drugs prescribed/tests arranged etcetc)	Routine or unplanned assessment or telephone

Appendix 16

Data Collection Form -WEEKLY MEDICAL REVIEW during radiotherapy

Patient Trial number **Patient Initials**
Date

Medications (current and past 7 days)

1.
2.
3.
4.
5.
6.
7.
8.
9.
10.

Medical Investigations (interventions) over the past 7 days

1.
2.
3.
4.
5.
6.
7.
8.
9.
10.

Number of days as Inpatient over past 7 days

Number of unplanned hospital visits over past 7 days

If attended hospital over past 7 days - Which Hospital?

Number of visits to GP over past 7 days

Appendix 17

Data Collection Form – 6 week post radiotherapy review
Patient Trial number **Patient Initials**

Current Medications

1.
2.
3.
4.
5.
6.
7.
8.
9.
10.

Medical Investigations (interventions) since completion of RT

1.
2.
3.
4.
5.
6.
7.
8.
9.
10.

Tumour assessment **CR** **PR** **SD** **DP**

Number of days as since completion of RT

Number of unplanned hospital visits since completion of RT

If attended hospital since completion of RT- Which Hospital?

Number of visits to GP since completion of RT

Appendix 18

Data Collection Form – Late phase medical monthly review
Patient Trial number **Patient Initials**
date

Current Medications

1.
2.
3.
4.
5.
6.
7.
8.
9.
10.

Medical Investigations (interventions) in last month (since last review)

1.
2.
3.
4.
5.
6.
7.
8.
9.
10.

Tumour assessment **CR** **PR** **SD** **DP**

Number of days as inpatient in last month

Number of unplanned hospital visits in last month

If attended hospital in last month - Which Hospital?

Number of visits to GP in last month

Appendix 2 : References

1. Bonner et al: A Randomised Phase 3 Trial To Compare Radiation Therapy Alone With Radiation Therapy And Concomitant Anti Egfr Antibody (Cetuximab) For Locally Advanced Squamous Cell Carcinoma Of The Head And Neck. New England Journal of Medicine, 354 (6): 567-578 2006.
2. Pignon J.P., Bourhis J, Domenge C:Chemotherapy added to loco-regional treatment for head and neck cancer: three meta-analyses of updated data. Lancet. 355(9208):949-55 2000
3. J. Bourhis: Impact Of Treatment Age In The Treatment Of Locally Advanced Head And Neck Cancer. Two Individual Patient Data Meta Analysis. J.C.O. Proc Soc Am Onc 24(18s):2006 Abs 5501
4. Forrastiere A et al: Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N.E.J.M. 349(22) : 2091-9 2003
5. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, Filiberti A, Flechtner H, Fleishman SB, de Haes JCJM, Kaasa S, Klee MC, Osoba D, Razavi D, Rofe PB, Schraub S, Sneeuw KCA, Sullivan M, Takeda F.
   The European Organisation for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. Journal of the National Cancer Institute 1993; **85:** 365-376
6. Fayers PM, Aaronson NK, Bjordal K, Groenvold M, Curran D, Bottomley A, on behalf of the EORTC Quality of Life Group.
   The EORTC QLQ-C30 Scoring Manual (3rd Edition).
   Published by: European Organisation for Research and Treatment of Cancer, Brussels 2001.

Appendix 2:Ammendments

a) Amendment 1 Page 13 version 12

Haematological Parameters at study entry: -

· Blood cell counts:

Absolute neutrophils > 1.5 x 10^9/L

Platelets > 100 x10^9/L

Haemoglobin > 12 g/dl

amended to

Haematological Parameters at study entry: -

· Blood cell counts:

Absolute neutrophils > 1.5 x 10^9/L

Platelets > 100 x10^9/L

Haemoglobin > 10 g/dl (may be correcetd by transfusion where appropriate)

Amendment 1 was required as Hb > 12 is too high for female entrants in to the study. The normal range for females commencing at a lower haemoglobin level

b) Amendment 2 page 12 version 12

3a. Quality of Life

The EORTC QLQ 30 and QLQ- H+N35 will be 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.
The patient may complete the QoL questionnaire at their hospital visit or they may take the questionnaire home and send it in to the hospital after completion. If the patient wishes to complete the questionnaire at the hospital visit a quiet private area should be provided to allow then to do so.
Will be amended to

3a. Quality of Life
The EORTC QLQ 30 and QLQ- H+N35 will be completed by the patient at study entry, on the last day of radiotherapy +/- 24 hours, at 6 weeks following completion of radiotherapy +/- 14 days and at 24 weeks +/- 14 days following completion of radiotherapy.
The patient may complete the QoL questionnaire at their hospital visit or they may take the questionnaire home and send it in to the hospital after completion. If the patient wishes to complete the questionnaire at the hospital visit a quiet private area should be provided to allow then to do so.

The amendment 2 was required to allow a little more flexibility in the timelines for assessments as the current protocol is too prescriptive to be practical.

Amendment 3 Appendix 5
Please see patient information sheet version 3 which now includes new 24hour help line telephone number

Amendment 4 Appendix19
A standard Serious Adverse Event (SEA) report form is preferred by the New Cross Hospital Trust for al Trust sponsored studies. Please see New SAE report form

e) Amendment 5
The study will run from September 24th 2008 to 31 Dec 2010 as the study we had delays in the delivery of study drug which has delayed recruitment.

Appendix 3:CV of Chief Investigator

CURRICULUM VITAE

Name:	
Dr. Caroline Brammer	
Present appointment: *(Job title, department, and organisation.)*	
Consultant Clinical Oncologist, Department of Oncology, Deanesly Centre, The Royal Wolverhampton Hospitals NHS Trust	
Address: *(Full work address.)*	
The Deanesly Centre, The Royal Wolverhampton Hospitals NHS Trust, New Cross Hospital, Wednesfield Road, Wolverhampton. WV10 0QP	
Telephone number:	**Email address:**
01902 695201	caroline.brammer@rwh-tr.nhs.uk
Qualifications:	
• Bachelor of Medicine – July 1991 • Bachelor of Surgery – July 1991 • MRCP (UK) Part 1, London – February 1993 • MRCP Part 2, London – June 1994 • FRCR (UK) Part 1, UK – June 1995 • FRCR Part 2, UK– April 1998	
Professional registration: *(Name of body, registration number and date of registration.)*	
GMC Full Registration Number - 3539091	
Previous and other appointments: *(Include previous appointments in the last 5 years and other current appointments.)*	
• Specialist Registrar in Clinical Oncology, Cookridge Hospital, Leeds – November 1996 – November 1999 • Registrar in Radiation Oncology, Auckland Hospital, New Zealand – December 1995 – November 1996 • Registrar in Radiotherapy and Clinical Oncology, Leicester Royal Infirmary – October 1994 – October 1995 • Senior House Officer, Respiratory Medicine, Derby City General Hospital – August 1994 – October 1994 • Senior House Officer, Derby City General Hospital – February 1994 – August 1994 • Senior House Officer, Gastroenterology and General Medicine, Derby City General Hospital – August 1993 – January 1994 • Senior House Officer, Intensive Care and Haematology, Derby City General Hospital – February 1993 – July 1993 • Senior House Officer, Department of Medicine for the Elderly, Derby City General Hospital – August 1992 – January 1993 • House Officer, General Surgery, Chesterfield and N Derbyshire Royal Hospital – May 1992 – July 1992 • House Officer, Urology, Chesterfield and N Derbyshire Royal Hospital – February 1992 – April 1992 • House Officer, General Medicine and Hepatology, Royal Hallamshire Hospital, Sheffield – August 1991 – October 1991	
Research experience: *(Summary of research experience, including the extent of your involvement. Refer to any specific clinical or research experience relevant to the current application.)*	
I am Head and Neck cancer research lead for the Greater Midlands Cancer Research Network. I am currently recruiting patient for the following studies :, PET-NECK, Persephone, REACT, BIG-DCIS, Fragmatic, COSTAR I have entered patients into many multi-centre randomised trials. eg Trial of Radiation dose for stage 1 Non Hodgkin's Lymphoma ABC, ATAC, Big Lung Trial, CR07, Trial of Radiation dose for stage 1 Non Hodgkin's Lymphoma , SECRAB, START etc. I have been chief investigator for 2 completed local studies and am the UK chief investigator CONCRT 2.	
Research training: *(Details of any relevant training in the design or conduct of research, for example in the Clinical Trials Regulations, Good Clinical Practice or other training appropriate to non-clinical research. Give the date of the training.)*	
ICH/GCP Training, New Cross Hospital – 2011 QA Training, New Cross Hospital – 18th March, 2009	
Relevant publications: *(Give references to all publications in the last two years plus other publications relevant to the current application.)*	
1)The Acceptability of Open Access Follow-up Clinics Following Palliative Radiotherapy for Carcinoma of the Bronchus from a Clinician, Community Palliative Care and Patient Viewpoint. J.Adlard J.Joseph C.V. Brammer, G.E.GerrardClinicalOncology13(6):404-8,2001. 2) Primary CD 30 +ve anaplastic large cell lymphoma of the breast presenting in pregnancy. A Lengyel, J Adjogatse, R Mehra, C. Brammer, W Fuggle, E Jones, B Isgar.The Breast 11, 457-459,2002 3)Book Review: Principles and Practice of Brachytherapy using afterloading systems .C.Brammer. Clinical Oncology 2002 4)Early Radiotherapy related morbidity. Hartley A. Giridharan S. Begum G. Billingham L. Brammer C. .Radiotherapy & Oncology. 68(1):89-90, 2003 Jul.	

External Beam Radiotherapy in the Management of Differentiated Thyroid Cancer. Ford D, Giridharan s, Mc Conkey C, Brammer C, Watkinson JC, Glaholm J. Clinical Oncology, Sept 2003 Vol 15 (6) 337-342.

5)HIV associated hodgkins disase of th anal canal. S Hikkman, C Brammer. Clinical Oncology 17 (11) p69 , 2005

6)A Case of Hypersensitity Vasculitis after Vinorelbine Injection in a Patient with Metastatic Breast Cancer. D. Bilku, C Brammer . Clinical Oncology vol 19 – 363, 2007

7)Cost-Effectiveness of Docetaxel with Cisplatin/5FU versus standard treatment as induction chemotherapy followed by concurrent chemoradiation therapy in locally advanced squamous cell cancer of the head and neck:Anju Partan, Jeroen Jansen, Chris Evans, Pr Posner, Philippe Beltran, Caroline Brammer. Abstract no 6069 ASCO 2007

8)A Retrospective Comparison of Dose Intensity Between Weekly Cisplatin And 3-weekly Cisplatin Delivered Concurrently with Radical Radiotherapy For Locally Advanced Head and Neck Squamous Cell Carcinoma At New Cross Hospital, Wolverhampton: K.F. Ho, C.V. Brammer . Acta Oncologica 2008 1-6

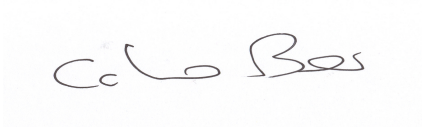
9)Consensus conference: Implementing treatment recommendations on yttrium-90 immunotherapy in clinical practice – Report of a European workshop, 15 January 2008
Pier Luigi Zinzani, Francesco d'Amore, Emilio Bombardieri, Caroline Brammer, José Gómez Codina, Tim Illidge, Wojciech Jurczak, Werner Linkesch, Franck Morschhauser, Elisabeth Vandenberghe, Achiel Van Hoof
European Journal of Cancer Vol44(3) 366-373,2008

10)Partan A, Posner MR, Brammer C , Beltran P, Jensen JP
Cost Utility analysis of doxectaxel as induction chemotherapy followed by chemoirradiation in locally advanced SCC H+N Head & Neck. 31(10):1255-62, 2009 Oct

11) Cetuximab (Erbitux) Plus Radiotherapy (ERT) Versus Concomitant Cisplatin Plus Radiotherapy (CRT) Within An NHS Oncology Unit (New Cross Hospital Wolverhampton. A randomised study: Abstract 22. Oral Presentation. 3rd Trends in Head and Neck Oncology Meeting. 3rd November 2011. Rome

12)Patients receiving concomitant Cisplatin and Radiotherapy require admission and non routine intervention due to acute toxicity more frequently than those receiving Cetuximab and Radiotherapy. Abstract 35 . Poster Presentation 3rd Trends in Head and Neck Oncology Meeting. 3rd November 2011. Rome

13) A Pilot Study Of Taxotere (Docetaxel), Cisplatin, And 5FU (TPF) In The Palliative Treatment Of Squamous Cell Carcinoma Of The Head And Neck. Abstract 33 . Poster Presentation 3rd Trends in Head and Neck Oncology Meeting. 3rd November 2011. Rome

Signature:	**Date:**
	13/01/2012

Appendix 4: Publications (poster)

Appendix 5:Patient Data (discontinued patients, excluded patients due to protocol violations)

EBRT 3: withdrawn after treatment phase as diagnosed with an oesophageal primary. Included in the acute phase analysis but excluded from late phase analysis

EBRT 5: withdrawn after treatment phase as died after treatment. Included in the acute phase analysis but excluded from late phase analysis

EBRT 7: withdrawn after acute phase as developed metastatic disease. Included in the acute phase analysis but excluded from late phase analysis