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Original Article

Cetuximab: a critical appraisal of a novel development in the treatment of squamous cell carcinoma of the head and neck

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Abstract

Recently published evidence has shown an improvement in locoregional control and a survival advantage in the treatment of squamous cell carcinomas of the head and neck (SCCHN) using cetuximab, a monoclonal antibody that inhibits the tumour-promoting mechanism of the epidermal growth factor receptor (EGFR). In a large randomised trial, cetuximab was delivered concurrently with radiotherapy and compared to radiotherapy alone in locally advanced SCCHN. The trial showed that the addition of cetuximab offers improved locoregional control and survival without enhancing acute toxicity compared to radiotherapy alone. These exciting results have the potential to change standard head and neck cancer practice, impacting on head and neck cancer services provided by oncology departments and multidisciplinary working.

This article aims to define the mechanism of action of cetuximab, critically appraise the evidence for the use of cetuximab within Oncology departments for SCCHN, and critically evaluate how cetuximab may impact on current practice. Future possibilities and trials to assess the use of cetuximab within clinical practice will also be discussed.

Keywords

cetuximab; chemotherapy; head and neck; radiotherapy; squamous cell carcinoma

INTRODUCTION

In England and Wales, there are approximately 8,000 cases and 2,700 deaths attributed to head and neck cancers per annum.[1] These cancers arise from approximately 30 sites within the head and neck, and the majority are squamous cell carcinomas (SCCHN).[1] Surgery, radiotherapy (RT) and chemoradiation (ChemoRT) are the major modalities used for the curative treatment of SCCHN, and often a multimodality approach is required in the management of these cancers.[2–5] This involves complex treatment pathways for patients. Provision of this treatment is challenging for health authorities, requiring a specialist multidisciplinary team (MDT) to provide an appropriate standard of care.[1]

Patients often present with locally advanced disease.[1] Historically, patients have been treated primarily with surgery, and frequently surgery is followed by post-operative RT.[5] Surgical intervention can be extensive, and even with reconstruction and rehabilitation, it can severely

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affect patients' quality of life (QoL).[1,5] Despite these treatments, patients are still at high risk of treatment failure, and with current treatment modalities the 5-year survival for this patient group is approximately 40–50%.[2] Disease typically re-presents either locally, in lymphatic tissue or as systemic metastasis.[3] Currently, evidence suggests that chemoRT is the gold standard treatment for locoregionally advanced disease and treatment of post-operative disease with positive surgical margins, large-volume nodal disease and nodal disease with extracapsular extension.[5] The gains in improved local tumour control, organ preservation and survival advantage with chemoRT is tempered by increased acute toxicity of the mainly platinum-based chemoRT regimens.[5,6] Patients have to deal with debilitating acute toxicity in the hope of cure.[5]

The emergence of novel biological targeted therapies to treat SCCHN offers the possibility of improvements in locoregional control and survival after treatment. One such target is the epidermal growth factor receptor (EGFR), which is commonly expressed in SCCHN, with high levels of expression often denoting poor prognosis.[7] Cetuximab is a monoclonal antibody that binds to EGFR, blocking the cellular interactions essential to tumour cell growth.[7] A publication by Bonner et al.[8] concluded that cetuximab, in combination with high-dose RT, improves locoregional control and improves survival compared to RT alone. In addition, the acute side effects of treatment were not enhanced in the cetuximab arm of the trial compared to the RT-alone arm.

In March 2006, the United States Food and Drugs Administration (FDA)[9] approved the use of cetuximab with RT for inoperable SCCHN after the publication of evidence proving a survival benefit in locally advanced disease. Approval was also given for the use of cetuximab as a monotherapy for metastatic SCCHN where chemotherapy has failed. The National Institute of Clinical Excellence (NICE)[10] selected cetuximab for the treatment of head and neck cancers for fast track approval. Appraisal of cetuximab was issued by NICE in May 2007.[11] NICE refused approval for the clinical use of cetuximab, as it was deemed the evidence presented at the appraisal was insufficient. Two areas of uncertainty were highlighted within the trial data. The first related to the population of patients studied, which concentrated on those who were suitable for RT, rather than the patient group most likely to benefit from cetuximab, who are those patients not suitable for chemoRT. The second related to the use of altered fractionation RT rather than the standard daily fractionation used in the United Kingdom.[11] Despite this, the trial showed great potential for the use of cetuximab for advanced SCCHN, and the decision of the appraisal committee went to an appeal. The result of the appeal has been published and the initial findings of the NICE appraisal have been upheld.[12]

This article aims to define the mechanism of action of cetuximab, critically appraise the evidence for the use of cetuximab within Oncology departments for SCCHN, and critically evaluate how cetuximab may impact on current practice. Future possibilities for cetuximab within clinical practice will also be discussed.

BACKGROUND

Traditionally, SCCHN has been managed with a combination of surgery, RT and, more recently, chemoRT.[2] The inhibition of the biological mechanisms that promote tumour growth and repair is an emerging concept for SCCHN. Biological targets for therapeutic agents are generally identified by an increased expression that results in enhanced tumour activity, and often indicate a poorer clinical outcome.[13] In epithelial cancers such as SCCHN, EGFR is abnormally activated and often highly expressed.[14] EGFR is a transmembrane glycoprotein, with a critical role in tumour cell regulation and growth; it has extracellular domains that have the capability to bind to molecules playing an important role in cellular repair and the invasiveness of cells.[7]

Cetuximab is a monoclonal antibody that binds to the extracellular domain of EGFR resulting in downregulation, and thus inhibiting the role of EGFR in tumour growth and repair.[13] Cetuximab binding results in EGFR cell internalisation, preventing further stimulation by EGFR agonists and cancer cell growth.[7]

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The enhancement of the effect of RT by cetuximab[8] has shown to result from a different mechanism to chemotherapy. Chemotherapy is thought to inhibit repair of RT damage, to radiosensitise hypoxic cells, reduce tumour burden and aid synchronisation and redistribution of cells into the RT-sensitive phases of the cell cycle.[3] EGFR expression increases in the cells regularly exposed to fractionated RT.[15] The radiation-induced activation of EGFR aids repair from RT damage and tumour cell growth. Blocking EGFR with cetuximab diminishes the ability of the tumour cell to repair, increasing cell apoptosis.[15] Thus the different biology of these mechanisms of action could lend themselves to combine chemoRT and cetuximab schedules,[16] particularly as cetuximab does not seem to enhance acute toxic side effects of RT.[8]

CRITICAL ANALYSIS OF CURRENT EVIDENCE

Published evidence supporting this novel treatment is minimal, yet the results of the trials to date are pertinent and cannot be ignored. Robert et al.[17] conducted a Phase I study of the use of cetuximab, in combination with radiation (cetuximabRT), for advanced head and neck cancers. Their work was based on the cellular biology and function of EGFR within tumour proliferation and cellular repair pathways, recognising the theory that a blockade of this tumour-promoting mechanism in combination with RT might improve control rates. The study aimed to test the safety and feasibility of administering cetuximab in combination with RT, and concluded that patients tolerated this combined treatment well. One patient suffered a reversible anaphylaxis to the antibody that prevented further infusions; other toxicities attributed to the addition of cetuximab included lethargy, a florid skin reaction outside the RT fields, nausea and fever. The study suggests that the addition of cetuximab appeared to enhance the RT toxicity; however, the modest sample size of 16 patients limited the ability to generalise the results of the trial into the SCCHN population.[17] This early work concluded that the results of safety and feasibility of cetuximabRT were encouraging, supporting further work in this novel therapeutic domain.[17]

Evidence published by Bonner et al.[8] compared high-dose radical RT plus cetuximab with RT alone for locoregionally advanced SCCHN. Both study arms included three RT fractionation regimes. The primary endpoint of the trial was SCCHN locoregional control. The trial randomised 424 patients, 213 received RT and 211 received cetuximabRT. The results showed an improvement in locoregional control of ~10 months (14.9–24.4 months) and in overall survival of ~20 months (29.3–49 months) in the cetuximabRT arm of the study. However, only 44% of patients within the trial were treated as stipulated in the methodology. Of the remainder, 31% received treatment with minor variation and 12% received treatment with acceptable major variation.[8] These deviations from the methodology were not explained within the publication, thus preventing independent evaluation of the effects on treatment outcomes, detracting from the impact of the results. The acute toxicity recorded in the cetuximabRT arm was comparable to the RT-alone arm, indicting that the addition of cetuximab has a survival advantage without enhancing the acute side effects of treatment.[8] This is a very encouraging result, offering a superior outcome for SCCHN patients without the expense of enhancing acute side effects.

Unfortunately, a comparison of chemoRT, the current gold standard treatment for this patient group, with cetuximabRT has not been published. This leaves questions unanswered as to the benefits of replacing chemoRT schedules with the cetuximabRT regimen. This opinion was echoed by Posner[6] who recognised that a lack of direct comparison with chemoRT, and the inconsistency of RT treatments used within the Bonner et al.[8] trial, made it difficult for oncologists to draw clinical inference on the use of cetuximab on outcomes. Posner surmised that clinicians should note that individual chemoRT trials have produced greater improvement than that recorded with cetuximabRT, and Phase III direct comparative studies are required to draw conclusive evidence.[6] Merck Oncology suggests that the

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cetuximab combination may offer an advantage over chemoRT.[15] It could be argued that if chemoRT and cetuximabRT outcome figures are comparable, then the reduced toxicity with the cetuximab regime would sway clinical practice towards cetuximabRT; however, this data are not available yet and ethically clinicians are unlikely to compromise survival by choosing cetuximabRT for the advantage of reduced toxicity if chemoRT is possibly more effective. In addition, the use of cetuximab has not been approved by NICE at this time.[12]

Cetuximab is under investigation in combination with chemoRT schedules for advanced SCCHN.[7] The mechanism of action of cetuximab indicates that a combined treatment may further improve survival. Pfister et al.[7] aimed to test if the addition of cetuximab could improve outcomes in combination with an existing chemoRT schedule. The study was stopped early with patient safety concerns following five significant adverse events. Although the adverse events were not directly attributed to cetuximab, the review of the trial stipulated that further information was required regarding the additional toxicity of cetuximab in combination with toxic chemoRT regimens before additional investigation is undertaken. The report recognised that the adverse events could be linked to co-morbidities common to the SCCHN patient group.[7] Despite early closure of the trial, the tumour control data on the 16 assessable patients are encouraging for a population with mainly stage IV disease,[7] justifying further investigation once safety is assessed.

There are areas regarding the use of cetuximab that are unexplored within large randomised trials and in the literature. Future investigations include direct comparison of the outcomes from cetuximabRT 'v' chemoRT regimen, clear indication to which RT dose and fractionation schedules the addition of cetuximab is most effective, and whether chemoRT with cetuximab will be safe to deliver resulting in improved outcomes. In addition to quantitative-based research, qualitative studies focusing on patient experience and QoL are required for a well-balanced perspective on the impact of this novel treatment.

IMPACT ON PRACTICE

The technical aspects of SCCHN RT treatment are complex and challenging to plan and deliver. This is further complicated by a patient group who, as a result of their disease, co-morbidities, and the effects of treatment toxicity, are very demanding to manage. The addition of concurrent chemotherapy to RT improves survival rates by 8% at 2 and 5 years,[18] but this comes at the expense of enhanced toxicity.[5,6] Within the authors department, the delivery and increased toxicity of chemoRT places additional demands on departmental resources and staffing. Linked with departmental pressures are the aims of the NICE Improving Outcome Guidance for Head and Neck Cancer,[1] who centralise their recommendation around improving survival, patient experience and QoL for patients. Within a busy service, these guidelines place emphasis on adequate provision for disease management, post-treatment rehabilitation and patient support services.

From a departmental and patient perspective, cetuximab may be more straightforward to deliver and require less time spent in hospital than the current chemoRT regime. The King's Fund[19] projections reported that oral administration of molecular therapies could reduce inpatient and day case costs. The projection acknowledges that oral drugs are often more expensive than intravenous (IV) infusions, and it is hoped that savings made on administration and ease of delivering oral drugs may counter-balance increased expenditure on the purchase of the drugs.[19] Despite cetuximab requiring eight IV infusions, over 8 weeks, there could be administrational savings for the cetuximab versus cisplatin regimen. The initial cetuximab infusion is over 120 min, with subsequent infusions over 60 min.[15] An additional monitoring period of 1-hour post-infusion is recommended, as cetuximab carries a risk of allergic reaction.[15] One of the frequently used SCCHN chemoRT regimes uses six weekly day case cisplatin infusions requiring admission for 6–7 hours per cycle. By comparison, the cetuximab regime would save bed space, staff time and patient time spent in the department. This could increase capacity in a service stretched to provide adequate cisplatin provision. Additional

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cost savings in the cetuximab regime result from the reduced requirement of expensive anti-emetics. However, cetuximab is known to cause an extensive acne form rash;[8] it is possible that savings made in analgesic and anti-emetic prescriptions associated with cisplatin may be replaced by antibiotics and skin care to treat this rash.

If RT reactions are not exacerbated by the addition of cetuximab,[8] pharmacological expense and medical/advanced practitioner/therapy radiographer/nursing time spent managing toxicity and supporting patients may be reduced. The need to admit patients towards the end of treatment for toxicity management may also reduce costs, as would a reduction in the requirement for enteral feeding. Unscheduled gaps during RT are occasionally required to allow acute toxicity to subside; prolongation of radical SCC RT courses have been shown to be detrimental to treatment outcome;[20] thus if toxicity resulting from chemoRT is reduced by treating with cetuximabRT, gaps may be avoided. Cetuximab requires infusion on the same day as RT, without the need to time the RT delivery,[15] unlike the concurrent cisplatin with RT regimen that requires a 2-hour gap between the end of the cisplatin infusion and the delivery of RT. Thus cetuximabRT may also reduce the problems associated with delayed cisplatin infusions impacting on RT treatment time, and the consequent overtime expenditure for staff to deliver RT out of hours. Timely delivery of treatment could result in more patients being treated with cetuximabRT each day within the department. These savings may help to balance the cost of cetuximab, which costs approximately £5700 + VAT for an 8-week course; additional costs include the antihistamine recommended as pre-medication.[15]

NICE proposed that provision for chemoRT should be made available to patients with advanced SCCHN who are fit enough to tolerate the treatment.[1] To be eligible for chemoRT, patients need a good performance status and ≤70 years old.[5] In practice, this still leaves a significant number of patients with advanced SCCHN who are not eligible for chemoRT. It is in these older, less fit patients that the evidence points to the possibility of the cetuximabRT combination. In the Bonner et al. trial,[8] the median age of the patient population in the RT arm was 58 years (range 35–83 years) and in the cetuximabRT arm 56 years (range 34–83 years); performance status was measured on the Karnofsky scale and ranged from 60 to 100. Performance status was evenly distributed between the two arms of the trial. In the publication, age and performance status were not correlated with toxicity scoring; therefore, it is not possible to determine if the older patients and less fit patients were the group who experienced the higher-grade toxicities reported. However, this patient group currently tolerate RT regimes well, and potentially the addition of cetuximab will improve outcomes without enhancing currently observed toxicity.

Once evidence and approval to use cetuximab is in place, the challenge is then for funding bodies such as Primary Care Trusts in the United Kingdom to allocate money for the provision of cetuximab in addition to RT, where currently concurrent treatment is not provided for this patient group. Justification of this expenditure and approval for funds is a lengthy process. Patient selection to receive new targeted therapies is essential to justify the costs and the use of limited resources. Posner[6] highlighted that the advantage in the cetuximabRT arm appeared to be associated predominantly with oropharyngeal tumours rather than hypopharynx and laryngeal tumours. Further trial data in this area may aid future clinical decision-making as to which patients will most benefit from cetuximabRT as opposed to chemoRT or RT alone. Kings Fund[19] acknowledged that the release of each new molecular targeted therapy is often associated with decisions regarding funding and eligibility. Patient selection is based on clinical reasoning, given the resources available; however, the portrayal of new cancer therapies as 'miracle cures' stimulates patient expectations to receive these novel therapies, possibly compromising the doctor–patient relationship.[19]

From an advanced practice perspective, cetuximabRT holds the potential to impact on departmental practice, possibly enhancing patient outcomes, simplifying patient pathways, without increasing toxicity management. Professional time dedicated to organisational

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aspects of chemoRT and unpredictable consultations associated with toxicity management could be reduced and re-allocated within the head and neck service if cetuximabRT is proved to be equal to, or more successful, in improving outcomes than chemoRT. These time and resource savings would also impact on other specialist services provided by allied professionals in dietetics, nursing and speech and language therapy that support SCCHN patients through treatment. Pressure on RT treatment staff would be alleviated, as the timing issues around chemoRT may be reduced, and minimise the referrals for crisis management associated with the levels of toxicity seen with the chemoRT schedules. Time, resource and cost evaluation will remain inconclusive until cetuximab has been trialed extensively in clinical settings and formal analysis has been made.

Opportunity for role extension could be embraced within current head and neck cancer advanced practice, including possible involvement in much needed clinical trials. This would embrace recommendations by the Royal College of Radiologists.[21] Their skills mix guidance promotes evaluation of the workforce and specialist training to enable cancer services to develop from traditional models. In turn, this encourages the exploration of new ways of working to facilitate change and provision of new treatments for patients within NHS cancer services. This would also offer the prospect of valuable learning experiences, enhanced continuing professional development, and the personal satisfaction linked with the aim of improving patient outcomes and treatment experience.

CONCLUSION

Cetuximab, in combination with RT and chemoRT regimes for SCCHN, is a novel development. The prospect of cetuximabRT to improve locoregional control and survival compared to RT alone, without enhancing toxicity, is an exciting prospect for head and neck cancer service providers. Large prospective randomised trials are required to investigate the treatment outcome and the safety of cetuximab verses the outcome and safety of the current gold standard treatment. Areas to explore include direct comparison of cetuximabRT 'v' chemoRT for different tumour sites within the head and neck, evaluation of locoregional control, survival advantage and QoL analysis of cetuximab with various RT fractionation schedules and investigation of combined chemoRT with cetuximab regimes. In addition, exhaustive economic evaluation is also required. Extensive prospective quantitative and qualitative research is needed to assess acute and late functional and QoL outcomes for this patient group for balanced evaluation of this drug. The results of these trials have the potential to impact on head and neck service provision, treatment outcome for SCCHN patients and improve practice. This in turn may offer opportunities for role extension within the head and neck MDT.

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