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Review

Cetuximab in the management of locoregionally advanced head and neck cancer: Expanding the treatment options?

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ABSTRACT

The treatment of locoregionally advanced squamous cell carcinoma of the head and neck (SCCHN) has evolved in recent years as a consequence of a better understanding of the potential benefits associated with altered radiation fractionation regimens, concurrently administered chemotherapy and radiotherapy (chemoradiotherapy) and induction chemotherapy. Concurrent chemoradiotherapy is a treatment option for technically resectable disease, where functional morbidity precludes the use of surgery. Induction chemotherapy followed by radiotherapy may also be used in this setting, and has been validated for larynx preservation. Concurrent chemoradiotherapy is a standard treatment approach for medically fit patients with locoregionally advanced unresectable disease. However, the toxicity burden of additional chemotherapy in both the concurrent chemoradiotherapy and induction chemotherapy settings can have implications for treatment compliance and may impede the administration of chemotherapy and/or radiotherapy to schedule. The epidermal growth factor receptor (EGFR)-targeted IgG1 monoclonal antibody, cetuximab (Erbitux®), has shown significant clinical benefits in the treatment of both locoregionally advanced and recurrent and/or metastatic SCCHN. A phase III study in locoregionally advanced disease demonstrated significant improvements in locoregional control and progression-free and overall survival with cetuximab plus radiotherapy compared with radiotherapy alone, and overall survival benefits were maintained at 5 years. The addition of cetuximab to concurrent chemoradiotherapy has been shown to be feasible in phase II trials and is being investigated in phase III trials. Preliminary evidence suggests that cetuximab could be incorporated into induction management strategies. Taken together, these data support an important role for cetuximab in the treatment paradigm for locoregionally advanced SCCHN.

1. Introduction

Head and neck carcinomas encompass a number of different tumour types affecting various anatomical sites. Cancers of the oral cavity, larynx and pharynx together account for around 5% of global cancer incidence.[1] Squamous cell carcinomas of the head and neck (SCCHN) are associated with a relatively high risk of developing second primary

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malignancies. The survival of patients with SCCHN is related to disease stage, performance status and comorbidities.[2–4]

In this review we discuss the role of the epidermal growth factor receptor (EGFR)-targeting IgG1 monoclonal antibody (MAb) cetuximab in current and future treatment strategies for locoregionally advanced SCCHN.

2. The role of radiotherapy and concurrent systemic therapy in locoregionally advanced disease

2.1. *Radiotherapy and concurrent chemoradiotherapy*

Locoregionally advanced SCCHN is generally treated with curative intent and aggressive treatment approaches are commonly used. Where disease is resectable, surgery followed by conventionally fractionated radiotherapy is a standard treatment option.[5] However, patients at a high risk of relapse may benefit from the post-operative administration of radiotherapy and concurrent chemotherapy (chemoradiotherapy) and this is now considered a standard of care in this setting.[5] Concurrent chemoradiotherapy is also an accepted treatment approach for tumours which are technically resectable, but where resection may lead to unacceptable functional morbidity,[5] and for locoregionally advanced, unresectable SCCHN.[5,6]

2.1.1. *Radiation and chemotherapy regimens*

Conventionally fractionated radiotherapy is a radiation standard in both the post-operative (2 Gy/fraction, total dose 55–66 Gy) and the definitive (2 Gy/fraction, total dose generally 70 Gy) settings. Ideally, radiotherapy should include 3D conformal or intensity-modulated regimens.[5] Where the tumour is no longer confined locally and/or there is nodal involvement, altered fractionation regimens, including various hyperfractionated and accelerated radiotherapy schedules, can be used. The survival benefits of accelerated regimens over conventional regimens are confined to those that do not markedly reduce the total dose of radiation.[7] Conventional radiation fractionation forms the basis of standard concurrent chemoradiotherapy schedules. Although adding chemotherapy to altered fractionation schedules significantly improves survival,[7,8] the possibility that combining chemotherapy with altered fractionation regimens will add to the already increased acute toxicity associated with such regimens needs to be carefully evaluated.

The most commonly used chemotherapy agent in concurrent chemoradiotherapy is cisplatin. While a combination of 5-fluorouracil (5-FU) and platinum provides a good alternative to cisplatin monotherapy, outcome data favour the use of cisplatin monotherapy as the chemotherapy component of concurrent chemoradiotherapy.[6] A validated regimen for cisplatin is 100 mg/m^2 administered for 3 21-d cycles (cumulative dose of 300 mg/m^2) and delivered throughout the course of radiotherapy. Although other cisplatin regimens have been investigated (either reduction of the total dose or more frequent administration of cisplatin with the same total dose), none has yet shown superiority over the standard dosing schedule.

2.1.2. *Concurrent chemoradiotherapy and toxicity*

Despite its association with survival benefits, concurrent chemoradiotherapy has drawbacks. The substantial acute toxicity, including mucosal and haematological toxicities, associated with this approach is well documented.[9,10] Even within clinical trials, about one-third of patients receiving concurrent chemoradiotherapy are not able to receive the full dose of chemotherapy according to schedule.[8,10,11] Sub-optimal chemotherapy dosing may impact negatively on disease-free survival.[12] In addition, interruptions in radiotherapy can reduce tumour control[13] and can lead to an increase in cancer-related mortality.[14,15] Prolonged breaks in radiotherapy[10] and a prolonged overall treatment time[11] due to the acute toxicities associated with concurrent chemoradiotherapy have been reported. Substantial late toxicity has also been reported after concurrent chemoradiotherapy.[16] This late toxicity may compromise functional outcome as well as the possibility of salvage surgery, if requested.

It is clear that while concurrent chemoradiotherapy, incorporating the full recommended dose of platinum, typically improves the outcome of patients with locoregionally advanced SCCHN, treatment-associated toxicities may prevent some patients from receiving chemotherapy as scheduled. Sub-optimal chemotherapy dosing has recently been shown in a retrospective analysis to impact negatively on disease-free survival.[12] These data highlight the need for effective but better tolerated combinations of systemic therapy and radiotherapy to optimise the potential for long-term survival of these patients.

2.2. *Cetuximab plus radiotherapy*

The results of the multinational, phase III trial, reported by Bonner and colleagues demonstrated that the addition of cetuximab to radiotherapy significantly improved locoregional control, progression-free survival and overall survival compared with radiotherapy alone (Fig. 1) in patients with locoregionally advanced squamous cell carcinoma (SCC) of the oropharynx, hypopharynx or larynx.[17] Patients were randomised to receive definitive radiotherapy either alone or in combination with cetuximab (initial dose of 400 mg/m^2 followed by weekly doses of 250 mg/m^2). Physicians had the option to choose between one of three fractionated radiation regimens: once-daily, twice-daily or concomitant boost. The

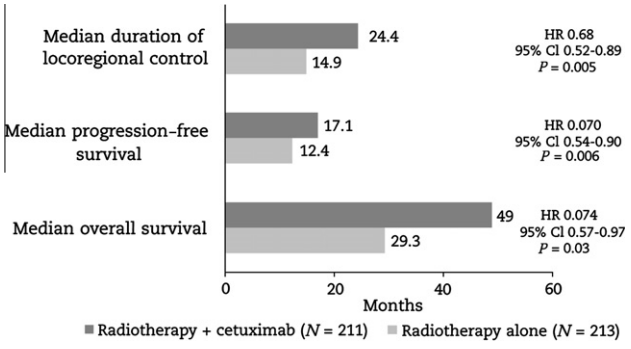

Fig. 1 – Radiotherapy plus cetuximab versus radiotherapy alone in locoregionally advanced SCCHN: efficacy results.[17] HR: hazard ratio and CI: confidence interval.

increase of 10 percentage points in the 3-year estimated survival rate with cetuximab (55.0% versus 45.0%) is very close to that seen in an earlier phase III intergroup study of standard radiotherapy alone versus concurrent chemoradiotherapy in locoregionally advanced disease.[9]

Importantly, the vast majority of patients (90%) in the Bonner trial were able to receive all planned doses of cetuximab. In addition, cetuximab did not interfere with the administration of radiotherapy dose and schedule, and compliance with radiotherapy was similar between the treatment arms.

A follow-up of the trial demonstrated that the survival benefit associated with cetuximab was maintained long-term. At 5 years, there was still a nine percentage point overall survival rate advantage for cetuximab plus radiotherapy compared with radiotherapy alone (45.6% versus 36.4%).[18]

It is tempting to use the Bonner data to speculate which groups of patients with locoregionally advanced disease will benefit most from the addition of cetuximab to radiotherapy. Indeed a subgroup analysis of the data was presented for both the original study and the follow-up analysis. However, the authors themselves acknowledge that the trial was not powered for such an analysis and urge caution in the interpretation of the resulting information.[18] The analysis suggests that the elderly and those with a poor performance status may derive less benefit from the addition of cetuximab to radiotherapy compared with younger patients and those with a good performance status.[18] This is not an unexpected finding, and increasing age has previously been shown to be significantly associated with a decreasing benefit of the addition of chemotherapy to locoregional treatment in locoregionally advanced head and neck cancer.[6] The elderly and those with a poor performance status present particular treatment problems, which necessitate continued investigation into treatment approaches that combine efficacy with good tolerability.

The data from the Bonner trial show that the combination of cetuximab and radiotherapy is significantly more effective than radiotherapy alone in locoregionally advanced disease and this combination is now accepted as a standard treatment approach for locoregionally advanced unresectable disease.[5] There are no randomised trials directly comparing the combination of cetuximab plus radiotherapy with concurrent chemoradiotherapy. Looking into this, a single institution retrospective comparison suggested that the combination of cetuximab and radiotherapy was perhaps as effective as concurrent chemoradiotherapy in terms of locoregional control and disease-specific survival.[19]

The addition of cetuximab to radiotherapy is also being investigated in the post-operative setting. A phase III trial is comparing intensity-modulated radiotherapy (IMRT) with IMRT with or without cetuximab in patients with resected, intermediate risk SCCHN (NCT identification number 00956007). Results are anticipated to be available in 2015.

2.2.1. *HPV-associated SCCHN*

Human papillomavirus (HPV) has been identified as an important aetiological factor in a distinct subset of SCCHN.[20–22] Oropharyngeal tumours are more frequently HPV-positive than other head and neck tumour types[20,21,23] and patients with HPV-positive oropharyngeal tumours have a significantly better outcome after concurrent chemoradiotherapy than those with HPV-negative tumours.[24–27] The association between HPV positivity and outcome has also been noted for SCCHN tumours other than those of the oropharynx.[28] The good prognosis of patients with HPV-positive SCCHN has led to speculation that concurrent chemotherapy may be too aggressive a treatment approach for these patients. Indeed, HPV-positive tumours respond better to radiotherapy alone than do HPV-negative tumours.[29] However, a single institution retrospective analysis of patients with tonsillar SCC suggested that radiotherapy alone was not an effective alternative to concurrent chemoradiotherapy in patients with HPV-positive disease, with a significantly higher rate of locoregional relapse and significantly lower rates of disease-free survival and overall survival in patients receiving radiotherapy alone compared with concurrent chemoradiotherapy.[30] The good tolerability of cetuximab plus radiotherapy in locoregionally advanced disease, compared with concurrent chemoradiotherapy, and the fact that it was associated with better outcomes than radiotherapy alone, suggest that this combination may be an option that could be considered for the management of HPV-positive SCCHN. However, further studies are necessary to substantiate this.

2.3. *Cetuximab plus concurrent chemoradiotherapy*

Considering the clinical benefits conferred by the addition of cetuximab to radiotherapy, and given that pre-clinical studies show that cetuximab enhances the effects of chemotherapy and radiotherapy,[31,32] it was a logical step to investigate the use of cetuximab combined with concurrent chemoradiotherapy in the treatment of locoregionally advanced SCCHN.

Kies and colleagues reported that the combination of cetuximab and either weekly cisplatin (30 mg/m^2) or docetaxel (15 mg/m^2) plus radiotherapy (60 Gy) was an effective approach for the post-operative management of patients with high-risk resected disease (positive margins and/or $\geqslant$2 nodal metastases or extracapsular nodal extension).[33] Results for both the cetuximab/cisplatin/radiotherapy and cetuximab/docetaxel/radiotherapy arms were promising, with 2-year disease-free survival (DFS) rates of 57% and 66% and 2-year overall survival rates of 69% and 79%, respectively. The authors compared the DFS results of this study favourably with the concurrent chemoradiotherapy arm of an historical control (Radiation Therapy Oncology Group [RTOG] study 9501),[34] although such comparisons should be interpreted with caution.

Studies have also looked at cetuximab plus concurrent chemoradiotherapy as definitive treatment.[35–37] In the Eastern Cooperative Oncology Group (ECOG) 3303 study cetuximab was added to cisplatin (75 mg/m^2 every 3 weeks) and radiotherapy (70 Gy over 7 weeks), followed by cetuximab maintenance therapy for 6 months. Treatment led to promising disease control in these patients with unresectable SCCHN, two-thirds of whom had oropharyngeal cancer.[35] The complete response rate among 60 eligible patients was 37%, with 2-year progression-free and overall survival rates of 44% and 66%, respectively. The most common grade 3/4 adverse events were haematological toxicities and mucositis. There was one treatment-related death.

A phase II study explored the use of alternating chemotherapy/radiotherapy, employing weekly cetuximab plus three 21-d

cycles of cisplatin (20 mg/m^2/d, days 1–5) and 5-FU (200 mg/m^2/d, days 3–5),[36] with radiotherapy administered (2 Gy/d, 5 d/week; total dose 70 Gy) in the two weeks between the end of chemotherapy and the start of the next cycle. Among 21 patients completing treatment, 95% received chemotherapy as planned, 86% received cetuximab as planned and all patients received radiotherapy as planned. The most common grade 3/4 toxicities among 24 evaluable patients were stomatitis (67%) and febrile neutropaenia (25%). Grade 2/3 rash was observed in 8% of patients and radiation dermatitis in 75%. There were two deaths on treatment, one due to pneumonia and another due to myocardial infarction. The response rate among 23 evaluable patients was 87% (15 complete responses/5 partial responses). After a follow-up period of 1–20 months, 15 patients were alive and disease-free.

A particular interest of cetuximab may lie in its tolerability profile, especially when compared with concurrent chemoradiotherapy. Phase II studies combining cetuximab with concurrent chemoradiotherapy have yielded promising data, but it is the results from phase III trials that will determine the role of cetuximab in this setting. In view of this, the results from the ongoing independent phase III trials being conducted by the RTOG (RTOG 0522) (concurrent chemoradiotherapy versus concurrent chemoradiotherapy plus cetuximab) and the Groupe Oncologie Radiotherapie Tête et Cou (GORTEC) 2007-01 trial (concurrent chemoradiotherapy plus cetuximab versus radiotherapy plus cetuximab) are awaited.

2.4. *Other EGFR targeted agents*

Cetuximab is the only targeted therapy that has demonstrated significant efficacy benefits in a phase III trial, increasing locoregional control, progression-free survival and overall survival. Cetuximab is also the only targeted therapy that is approved for the treatment of locoregionally advanced SCCHN. A number of randomised trials are being conducted with other EGFR-targeted therapies, both MAbs and tyrosine kinase inhibitors, in the setting of radiotherapy or chemoradiotherapy, with results expected in the coming years. For example, two phase III trials are ongoing, one that compares panitumumab plus accelerated radiotherapy with concurrent cisplatin plus conventionally fractionated radiotherapy (NCT identification number 00820248) and a Danish Head and Neck Cancer Group trial comparing the combination of zalutumumab and radiotherapy with treatment including concurrent chemoradiotherapy (NCT identification number 00496652). Other examples include three randomised phase II trials comparing concurrent chemoradiotherapy alone with concurrent chemoradiotherapy plus panitumumab (CONCERT-1, NCT identification number 00500760), erlotinib (NCT identification number 00410826) or lapatinib (NCT identification number 00387127).

3. A new treatment paradigm for locoregionally advanced disease: the sequential approach

3.1. *Induction chemotherapy*

The use of a sequential approach, whereby chemotherapy (induction chemotherapy) is administered prior to radiotherapy or concurrent chemoradiotherapy, is being evaluated as an alternative option for patients with locoregionally advanced, unresectable disease. This approach has already been validated in the setting of larynx preservation in patients with resectable disease, when induction chemotherapy is followed by radiation therapy in good responders.[38] Data from a subset analysis of patients with laryngeal and hypopharyngeal cancers enrolled in a trial of induction chemotherapy followed by concurrent chemoradiotherapy suggest that this option should also be considered.[39] The introduction of more effective induction chemotherapy regimens has led to suggestions that induction chemotherapy, used prior to radiotherapy/concurrent chemoradiotherapy, may have more beneficial effects on long-term survival than concurrent chemoradiotherapy alone, in part by reducing the risk of distant metastatic disease development. This sequential treatment approach may be particularly suited for the treatment of aggressive tumours which have a high likelihood of developing metastases.

Two randomised trials individually demonstrated a survival benefit with the use of induction with cisplatin/5-FU (PF) prior to locoregional treatment (radiotherapy with or without surgery) compared with locoregional treatment alone.[40,41] In one study, benefit was confined to patients with inoperable disease.[41] However, in a recently updated meta-analysis of data from 87 randomised trials, an indirect comparison showed a more pronounced survival benefit of concomitant chemotherapy compared with induction chemotherapy, when each was combined with locoregional treatment.[6] A direct comparison was possible in six trials and this indicated a similar trend in favour of the concomitant approach, although the difference did not reach statistical significance.[6] In terms of the preferred induction chemotherapy regimen, three phase III clinical trials have shown improved tumour responses[42] and survival benefits[43,44] with a triplet induction regimen of a taxane, platinum and 5-FU compared with PF.

It should be noted that the relative value of sequential and concomitant chemotherapy/radiotherapy in unresectable disease can only be assessed by a direct comparison of these two treatment approaches, and a number of randomised trials were set up to investigate this question. Two of these trials (the PARADIGM trial from the Dana-Farber Cancer Center and a joint Southwest Oncology Group [SWOG]/ECOG trial) were closed due to insufficient patient accrual. The phase III DeCIDE trial completed accrual in May 2009. From an initial estimated enrollment of 400 patients (200 per arm), which was later revised to 280 patients, accrual to the trial was closed at 285 patients. The first available results from a phase III trial looking at sequential versus only concurrent chemotherapy administration in unresectable SCCHN were reported at the 2009 annual meeting of the American Society of Clinical Oncology.[45] This was a three-arm trial in which patients received concurrent chemotherapy alone or preceded by induction chemotherapy with either PF or docetaxel plus PF (TPF). While the results suggested a favourable outcome for the sequential approach, methodological problems with the trial do not allow firm conclusions to be drawn. The main issue with the trial concerned the high, unexplained number of patients excluded from the efficacy analysis (9 [7%] in the concurrent chemotherapy arm and 77 [25%] in the induction

chemotherapy arms). An analysis of the intention-to-treat population is required to assess the relative efficacies of the treatment approaches. Other issues included the carrying out of an interim analysis while the trial was still recruiting patients, an increase in the planned sample size while the trial was in progress, and the change from the initial intention to compare the three arms of the trial to the subsequent comparison of the combined data from the induction chemotherapy arms with the concurrent chemoradiotherapy arm. Data from a randomised phase II trial in 101 patients with unresectable disease who received PF plus radiotherapy either alone or following 3 cycles of TPF induction chemotherapy[46] have suggested a potential advantage for sequential therapy, and this study is ongoing as a phase III trial. The data from these trials, either individually or combined in a meta-analysis, will ultimately provide an answer to the question of whether adding induction chemotherapy to concurrent chemoradiotherapy improves outcome compared with chemoradiotherapy alone.

3.1.1. *Induction chemotherapy and toxicity*

It is possible that the toxicity associated with induction chemotherapy may compromise the optimal administration of subsequent concurrent chemoradiotherapy. This is particularly relevant where platinum is part of the induction chemotherapy regimen, as administration of the full recommended dose of the platinum component of concurrent chemoradiotherapy may not be achievable.[47] Alternative therapy approaches, in both the induction and post-induction settings, need to be evaluated in these patients.

3.2. *Cetuximab in the post-induction setting*

The activity of cetuximab plus radiotherapy in locoregionally advanced disease, and its good tolerability profile, suggests that this combination would offer an effective treatment option post-induction chemotherapy.

A number of single-arm phase II trials have incorporated cetuximab into post-induction radiotherapy or concurrent chemoradiotherapy regimens.[48–52] To date, however, only the phase II TREMPLIN trial in resectable disease has compared post-induction cetuximab plus radiotherapy with concurrent chemoradiotherapy in a randomised setting.[47] This trial demonstrated that treatment with cetuximab plus radiotherapy following induction chemotherapy with TPF was at least as effective as cisplatin-based concurrent chemoradiotherapy according to the larynx preservation rate at 3 months. It is interesting to note that TPF-associated toxicity precluded seven potentially randomisable patients (6%) from receiving any further cisplatin treatment. These patients went on to receive radiotherapy alone, although in clinical practice they would have been eligible for treatment with cetuximab. In addition, three patients (5%) randomised to the cetuximab arm had reactions following the first administration of cetuximab (one patient reported cardiac palpitations, although there were no clinical or electrocardiographic signs, and two patients had allergic reactions), and did not continue treatment with cetuximab. Just under half of the patients in the cisplatin arm received the full post-induction protocol compared with nearly three quarters in the cetuximab arm (43% versus 71%). In addition, nine of the 58 patients (16%) in the cisplatin arm had renal dysfunction at the final trial assessment, precluding those patients from receiving any further platinum-based treatment.

The results from this trial[47] suggest that the combination of cetuximab and radiotherapy provides similar short-term rates of larynx preservation to platinum-based concurrent chemoradiotherapy, but with better overall tolerability and treatment compliance. Long-term efficacy and toxicity data should help to more clearly define the clinical benefits of this approach.

3.3. *Cetuximab in the induction setting*

Cetuximab has also been investigated as a component of different induction regimens.

In a phase II study, single-agent cetuximab induction therapy was administered prior to cetuximab plus concurrent chemoradiotherapy (paclitaxel/carboplatin) in patients with advanced disease[49] (Table 1). The response rate for cetuximab induction therapy was 35% among 23 patients, with a disease control rate of 96%. Grade 3 toxicities over the study included rash in 9% of patients.

Phase II studies have also investigated the addition of cetuximab to doublet induction chemotherapy with platinum and a taxane.[52–54] In patients with potentially operable SCCHN, 6 cycles of induction therapy with cetuximab plus paclitaxel and carboplatin followed by cetuximab plus concurrent chemoradiotherapy (paclitaxel/carboplatin) and maintenance cetuximab were associated with a complete pathologic response rate of 63%, and a post-concurrent chemoradiotherapy response rate of 98%.[52] In another study, induction chemotherapy with cetuximab, paclitaxel and carboplatin was followed by risk-based radiotherapy, concurrent chemoradiotherapy or surgery.[54] Induction therapy was associated with a 96% response rate. The 3-year progression-free and overall survival rates were 87% and 91%, respectively. In a third study, 3 cycles of docetaxel, cisplatin and cetuximab induction therapy were followed by concurrent radiotherapy/platinum/cetuximab.[53] The response rate to induction therapy was 86% and all patients had disease control.

The effects of adding cetuximab to induction therapy with the triplet TPF regimen have been reported by a number of investigators.[51,55,56] In a retrospective analysis of patients receiving TPF plus cetuximab induction therapy, there was response rate of 78% at the primary tumour site.[56] In a phase II study, cetuximab was incorporated into induction TPF chemotherapy and into the subsequent radiotherapy regimen for patients with unresectable SCCHN.[51] After 4 cycles of induction therapy, the overall response rate was 78% and the disease control rate was 84%. A substantial number of patients were given a reduced dose of docetaxel after cycle 1. Nevertheless, there were two adverse event-related deaths: one due to hepatic toxicity another due to febrile neutropaenia. A phase I study investigated the maximum-tolerated dose of 5-FU (700, 850 and 1000 mg/m^2) for use in a combination of TPF plus cetuximab induction therapy in SCCHN, prior to platinum-containing concurrent chemoradiotherapy.[55] A 5-FU dose of 850 mg/m^2 was designated the maximum-tolerated dose in this study. Along with this lower 5-FU dose,

Table 1 – Cetuximab in induction therapy.

Treatment	Phase	N	Main primary tumour site	Response to induction therapy	Response after subsequent therapy	Grade 3/4 toxicities
Cetuximab monotherapy[49] *Induction*: Cetuximab monotherapy (4 weeks) *CRT*: *Potentially operable patients*: Cetuximab, paclitaxel 40 mg/m^2 and carboplatin AUC 1 (weekly for 5 weeks) plus radiation 45 Gy. If the biopsy was negative at this stage, patients received three additional weekly doses of cetuximab, paclitaxel and carboplatin with boost RT 22–27 Gy *Inoperable patients*: Cetuximab, paclitaxel and carboplatin; radiation 66.6–72 Gy for 8 weeks After CRT, all patients received maintenance cetuximab for 24 weeks	II	29	N = 29 Larynx 41% Oral cavity 34%	N = 23 ORR 35% (1 CR/7 PR) DCR 96%	N/R	***After induction*** N = 23 *Grade 3*[a] Dysphagia 44% Mucositis 26% RT dermatitis 18% Rash 9% *Grade 4* Hypokalaemia 4% Ischaemic colitis 4%
Cetuximab/paclitaxel/carboplatin[52] *Induction*: Cetuximab, paclitaxel 90 mg/m^2/week, carboplatin AUC 2/week for 6 weeks (weeks 1–8) Weeks 7–8 restaging *CRT*: Cetuximab, paclitaxel 30 mg/m^2/week, carboplatin AUC 1/week; radiation (total dose 50 Gy in 25 fractions) (weeks 9–13) *Biopsy-positive*: Salvage surgery *Biopsy-negative*: CRT continued (68–72 Gy) Maintenance cetuximab for 6 months	II	74	Tonsil 33%	N = 66 63% (complete pathologic response)	N = 31 98% (complete pathologic response) After continued CRT, biopsies in all 55 evaluable patients were negative	***Overall*** *Grade 3 (>5%)* Mucositis 30% Leucocytes 23% Neutrophils 17% Dysphagia 15% RT dermatitis 13% Anorexia 12% *Grade 4 (>5%)* Neutrophils 14% Leucocytes 6%
Cetuximab/paclitaxel/carboplatin[54] *Induction*: Cetuximab, paclitaxel 135 mg/m^2/week, carboplatin AUC 2/week for 6 weeks *RT/CRT or surgery*: Various	II	47	Oropharynx 87%	N = 47 96%	N = 47 70%	***After induction*** N = 47 (AE > 5%) *Grade 3* Rash/folliculitis 45% Neutropaenia 19% Diarrhoea 9% ***After subsequent therapy*** N = 47 (AE > 5%) *Grade 3* Mucositis 77% Anorexia 6% Dehydration 6% Nausea/vomiting 6%

Table 1 – *Continued*

Treatment	Phase	N	Main primary tumour site	Response to induction therapy	Response after subsequent therapy	Grade 3/4 toxicities
Cetuximab/docetaxel/cisplatin[53] *Induction*: Cetuximab (weekly), docetaxel 75 mg/m^2 (d1), cisplatin 75 mg/m^2 (d1), every 21 d for 3 cycles *CRT*: Cetuximab (weekly), cisplatin 30 mg/m^2 (weekly) or carboplatin AUC 1.5 for patients with cisplatin-related toxicity; radiation 70 Gy, for 7–8 weeks Maintenance cetuximab for 6 months	II	39	Oropharynx 59%	N = 37 86% (2 CR/30 PR) DCR 100% Preliminary survival: 1-year OS 92% 2-year OS 88% 1-year PFS 80% 2-year PFS 80%	N = 33 100%	***After induction*** N = 39 (AE > 5%) *Grade 3/4* Neutropaenia 77% Neutropaenic fever 10% Hypomagenesaemia 10% Infection 8% ***After CRT*** N = 33 (AE > 10%) *Grade 3/4* Mucositis 51% Dysphagia 48% Neutropaenia 36% Hypomagnesaemia 36% Dermatitis 27% Infection 18% Anaemia 15% Thrombocytopaenia 12% Fatigue 12%
Cetuximab/docetaxel/cisplatin/5-FU[56] *Induction*: Cetuximab, docetaxel 75 mg/m^2 (d1), cisplatin 75 mg/m^2 (d1), 5-fluorouracil 750 mg/m^2 (d1–3) every 3 weeks *CRT*: Various regimens	Retrospective analysis	23	Oropharynx 61%	N = 23 Primary site: 78% Lymph nodes: 80%	At the time of meeting report, 14 of 23 patients were alive and disease-free	***After induction*** N = 21 (AE > 5%) *Grade 3* Neutropaenia 35% Neutropaenic fever 13% Anaemia 13% Diarrhoea 13% Mucositis 9% *Grade 4* Infusion reaction 17%
Cetuximab/docetaxel/cisplatin/5-FU[51] *Induction*: Cetuximab (d1, 8, 15), docetaxel 75 mg/m^2 (d1), cisplatin 75 mg/m^2 (d1), 5-FU 750 mg/m^2 24-h infusion (d1–5), X4 cycles *Post-induction*: Cetuximab + concomitant boost accelerated RT (total dose 69.9 Gy in 41 fractions) for 8 weeks	II	50	Oropharynx 48% Hypopharynx 34%	N = 50 After 4 cycles ORR 78% (12 CR/27 PR) DCR 84%	N/R	***After induction*** N = 50 (AE > 5%) *Grade 3/4* Neutropaenia 26% Febrile neutropaenia 24% Diarrhoea 14% Stomatitis 14% Skin toxicity 8% Dysphagia 6% Asthenia 6%
Cetuximab/docetaxel/cisplatin/5-FU[55] *Induction*: Cetuximab (weekly), docetaxel 75 mg/m^2 (d1), cisplatin 100 mg/m^2 (d1), 5-FU 700, 850 or 1000 mg/m^2 (d1–4) every 3 weeks for 3 cycles *CRT*: Various platinum-containing regimens	I (5-FU-dose finding)	30	Oropharynx 71%	N = 28 100% (22 CR/6 PR)	At a median follow-up of 8 months, 24 patients (85%) were alive with no recurrence	***DLTs at the MTD of 5-FU (850 mg/m^2)*** N = 13 *Grade 3* Febrile neutropaenia (N = 1) Mucositis (N = 1) Diarrhoea (N = 1) At the MTD of 5-FU (850 mg/m^2), one patient had grade 3 acne-like rash

N: number of patients; N/R: not reported; ORR: overall response rate; CR: complete response; PR: partial response; CRT: concurrent chemoradiotherapy; DCR: disease control rate; AE: adverse events; AUC: area under the concentration-time curve; RT: radiotherapy; OS: overall survival; PFS: progression-free survival; DLT: dose-limiting toxicity; and MTD: maximum-tolerated dose. Cetuximab was administered at an initial dose of 400 mg/m^2 followed by subsequent weekly doses of 250 mg/m^2.

[a] Toxicities shown are those reported.

and based on the findings of the study, the investigators also recommended that cetuximab should be administered on days 1 and 8 of each 21-d TPF cycle, rather than the weekly administration specified in the study design. Across the 5-FU dose ranges investigated, all patients achieved a tumour response following induction therapy. All 28 patients were able to receive concurrent chemoradiotherapy.

Irrespective of the chemotherapy doses used, the response rates achieved with the addition of cetuximab to doublet and triplet chemotherapy regimens compare favourably with the 68% and 72% response rates reported with TPF in the large randomised trials that confirmed the superiority of TPF over PF as induction therapy.[43,44]

While the first available data are encouraging, further investigation is required to confirm the efficacy and safety of cetuximab combined with different induction chemotherapy regimens, in particular with the presently used TPF regimens.

4. Safety and tolerability of cetuximab

The most common adverse events observed with cetuximab are skin reactions, which may develop in more than 80% (any grade) of patients. Acne-like rash is the most frequently observed skin reaction. There is an indication from some studies in SCCHN that the severity of rash is associated with efficacy.[18,57,58] In the Bonner trial, in patients receiving cetuximab, the risk of death was significantly lower in patients developing grade 2 or higher rash than in those with grade 1 rash or no rash (hazard ratio 0.49, 0.34–0.72; $p = 0.002$).[18] As most patients receiving radiotherapy will develop radiation dermatitis, the effects of cetuximab on skin have focused interest on its safety when used together with radiotherapy.

In the Bonner trial, there was a significantly higher incidence of grade $\geqslant 3$ acne-like rash (17% versus 1%, $p < 0.001$) in cetuximab-treated patients.[17] However, there was no statistically significant difference between radiotherapy alone and cetuximab plus radiotherapy in the incidence of grade $\geqslant 3$ radiation dermatitis (18% versus 23%, $p = 0.27$). Moreover, the good compliance with the cetuximab/radiotherapy treatment regimen confirmed the observation that there was no substantial interruption of treatment due to skin toxicity.

A recent survey reported severe skin reactions occurring concurrently with radiation dermatitis within the irradiated field of patients receiving cetuximab and radiotherapy.[59] The development of skin reactions may be influenced by a number of factors, including radiation technique, methods of assessment and comorbidities. Optimal skin management in this setting plays a key role. When skin reactions do occur, they should be managed promptly and effectively to ensure continued compliance with treatment, and guidelines are available for the management of acne-like rash in patients receiving EGFR targeted therapies with radiotherapy.[60] There is evidence to suggest that the management of these skin reactions improves as physicians gain experience in treating them.[61]

The clinical benefit observed with cetuximab in the Bonner trial was achieved without exacerbation of other known radiotherapy-associated toxicities, including mucositis, xerostomia and dysphagia. Approximately half of the patients in each group experienced grade $\geqslant 3$ mucositis.[17] In addition, a quality of life analysis of the data reported that the efficacy benefits of cetuximab were achieved without compromising a variety of aspects of patient quality of life, including social, cognitive, emotional, role and physical functioning, and global health status.[62]

The safety of cetuximab has also been investigated in patients with recurrent and/or metastatic SCCHN in the EXTREME study.[63] In this study, cetuximab plus platinum/5-FU was compared with platinum/5-FU and the safety profile of the study treatments were consistent with what was expected. The incidences of most grade 3/4 adverse events did not differ between the treatment arms, apart from skin reactions (9% for cetuximab plus platinum/5-FU versus <1% for platinum/5-FU), sepsis (4% versus <1%, respectively) and hypomagnesaemia (5% versus 1%, respectively). In addition, there were six grade 3/4 infusion-related reactions in the cetuximab arm compared with none in the chemotherapy-alone arm. According to the prescribing information, the combination of cetuximab and 5-FU may be associated with an increase in the frequency of cardiac events.[64]

The continued investigation of cetuximab plus chemotherapy, with or without radiotherapy, in locoregionally advanced disease, should provide more information regarding the adverse events seen with such combinations in this setting.

5. Conclusions

The role of cetuximab in the treatment of locoregionally advanced head and neck cancer continues to develop. The data from a phase III trial support the role of cetuximab plus radiotherapy as an effective treatment option for patients with locoregionally advanced SCCHN. Adding cetuximab to radiotherapy led to significant improvements in locoregional control and survival and these survival improvements were maintained long-term, with a nine percentage point advantage for cetuximab plus radiotherapy in the 5-year overall survival rate, compared with radiotherapy alone. The combination of cetuximab and concurrent chemoradiotherapy is currently being investigated in phase III trials. Incorporation of cetuximab into sequential chemotherapy and radiotherapy/chemoradiotherapy regimens is yielding interesting results. After induction chemotherapy, the combination of cetuximab and radiotherapy was better tolerated than platinum-based concurrent chemoradiotherapy with a similar short-term rate of larynx preservation. The clinical value of combining cetuximab with induction chemotherapy regimens is also being investigated.

Conflict of interest statement

J. Bourhis reports receiving advisory board honoraria from GlaxoSmithKline, Merck KGaA and sanofi-aventis. J.-L. Lefebvre reports receiving lecture and advisory board honoraria from Merck KGaA and sanofi-aventis. J.B. Vermorken reports receiving lecture and advisory board honoraria from Amgen, Boehringer Ingelheim, Lilly, Merck KGaA and sanofi-aventis.

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