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Cetuximab in the management of nasopharyngeal carcinoma – a narrative review

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Review Article

Dr M S Iqbal takes responsibility for the integrity of the content of the paper

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Abstract

Background. Concurrent chemotherapy with radiotherapy is the standard treatment for locoregionally advanced nasopharyngeal cancer. Cetuximab can be used in the treatment of head and neck squamous cell carcinoma. However, the randomised studies that led to approval for its use in this setting excluded nasopharyngeal cancer. In the context of limited data for the use of cetuximab in nasopharyngeal cancer in the medical literature, this review aimed to summarise the current evidence for its use in both primary and recurrent or metastatic disease.

Method. A literature search was performed using the keywords 'nasopharyngeal neoplasm', 'cetuximab' and 'Erbitux'.

Results. Twenty studies were included. There were no randomised phase III trials, but there were nine phase II trials. The use of cetuximab in the treatment of nasopharyngeal carcinoma has been tested in various settings, including in combination with induction chemotherapy and concurrent chemoradiotherapy, and in the palliative setting.

Conclusion. There is no evidence of benefit from the addition of cetuximab to standard management protocols, and there is some evidence of increased toxicity. There is more promise for its use in metastatic or locally recurrent settings. This review draws together the existing evidence and could provide a focus for future studies.

Introduction

Nasopharyngeal carcinoma (NPC) is considered a distinct entity from other head and neck carcinomas because of its association with Epstein–Barr virus, its aggressive locoregional behaviour and the relatively higher risk of distant metastases.[1] Given the anatomical location and radiosensitive behaviour of the tumour, radiotherapy (RT) has been the mainstay of local treatment.[2] Since the publication of the Al-Saraff *et al.* study in 1998,[3] concurrent chemoradiotherapy has gradually become the standard treatment for locoregionally advanced NPC.

Epidermal growth factor receptor, a member of the ErbB family of receptor tyrosine kinases, is expressed in many epithelial carcinomas. It has been reported that epidermal growth factor receptor is expressed in more than 85 per cent of NPC cases.[4,5] Studies have also suggested that the expression of epidermal growth factor receptor is independently associated with poor clinical outcomes.[5,6] Bonner *et al.* showed that cetuximab, an immunoglobulin G1 monoclonal antibody against the ligand-binding domain of epidermal growth factor receptor, is efficacious in squamous cell cancers of the head and neck region.[7] However, patients with primary NPC were not included in this phase III trial. Similarly, in recurrent and/or metastatic squamous cell head and neck cancer patients, the addition of cetuximab to chemotherapy was shown to increase response rate, progression-free survival and overall survival in comparison to chemotherapy alone.[8] However, primary NPC was an exclusion criterion. High quality evidence for the use of cetuximab in NPC would appear lacking. We aimed to examine the available literature on the use of cetuximab in NPC.

Materials and methods

Published data for this review were identified by searching PubMed-Medline and Embase databases, and the Cochrane (reviews and economic evaluations) library, from 1997 to the present day (a 20-year period; the date of the search was 11th August 2017, with a re-run on 23rd August 2018). The Medical Subject Heading terms and keywords used in the search were: 'nasopharyngeal neoplasm', 'cetuximab' and 'Erbitux'. A professional librarian conducted the literature search, and two authors (MSI and AT) analysed the list to identify suitable studies. All pertinent articles were retrieved, and selected studies were considered for this review. The references were also manually searched to identify other

Source	Results found (original + re-run search)	Discarded (included removal of duplicate & non-applicable records)	Final results
Medline	20 + 14	16	18
Embase	53 + 33	57	29
Cochrane reviews & economic evaluations	25 + 21	38	8

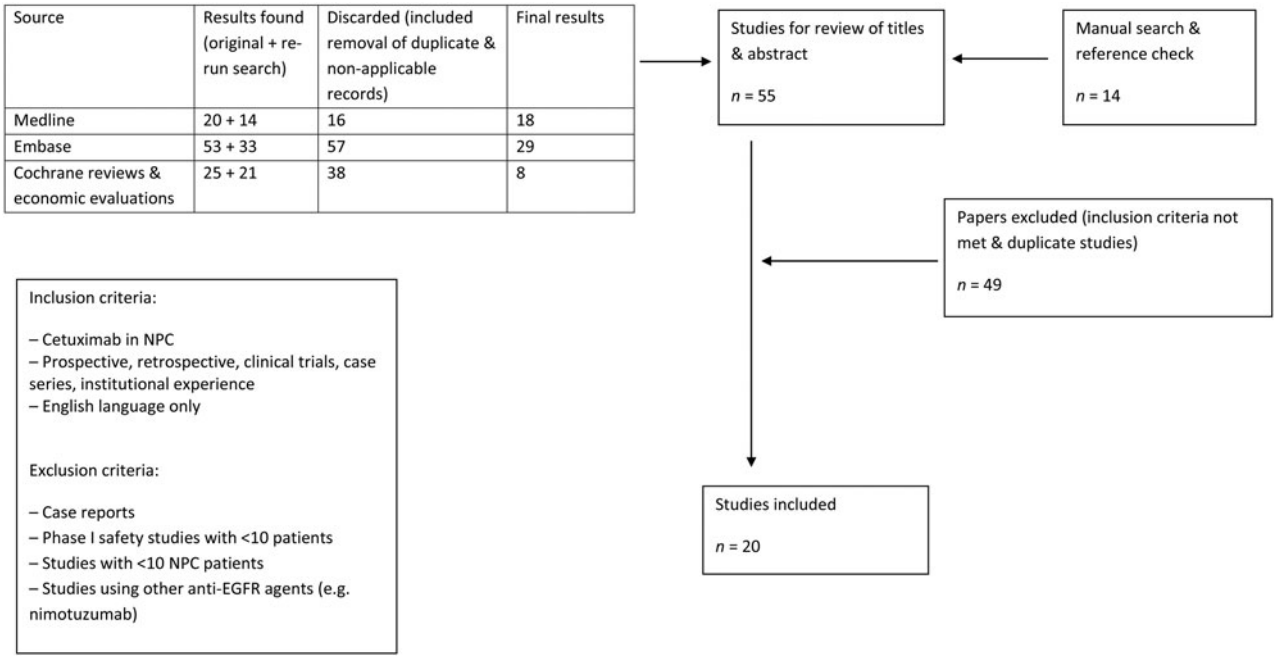

Fig. 1. Flowchart of the literature search. NPC = nasopharyngeal carcinoma; EGFR = epidermal growth factor receptor

relevant studies. One author (MSI) collected the literature data and another author (AT) reviewed them for quality assurance. A flow chart of the search is shown in Figure 1.

In this review, the selected studies were allocated either to locally advanced or to recurrent or metastatic nasopharyngeal carcinoma groups. For each group, the results are summarised in terms of subgroups based on the sequence of cetuximab use.

Results

The literature search identified 55 studies for review based on titles and abstracts. A manual search of references identified 14 further studies. Twenty studies were included in the final review (Figure 1).[9–28] The inclusion and exclusion criteria are also shown in Figure 1. Given the heterogeneous nature of the studies, and the fact that many studies were available in abstract form only with variable reporting on outcomes, it was not possible to perform either a meta-analysis or statistical analyses of the pooled data.

There were no randomised controlled phase III trials. Nine phase II trials were identified.[9–11,15,18,20,24–26] Of 20 selected studies, 5 were presented in the form of abstracts only. The findings of the selected studies that describe the use of cetuximab in nasopharyngeal carcinoma (NPC) are summarised in Tables 1–8.[9–28]

Locally advanced nasopharyngeal carcinoma

Cetuximab with chemoradiotherapy

Four phase II trials,[9–11,15] one prospective study[14] and four retrospective studies[12,13,16,17] assessed the effects of adding cetuximab to concurrent chemoradiotherapy. In the 4 phase II trials, the number of patients enrolled ranged from 30 to 100. A standard dose of cetuximab (initial loading dose of 400 mg/m^2 followed by 250 mg/m^2 on a weekly basis) was added to cisplatin-based concurrent chemoradiotherapy. In two of these phase II studies, a variable number of patients also received neo-adjuvant or adjuvant chemotherapy. Grade 3 or 4 mucositis was the most common toxicity, with incidence ranging from 71 per cent to 87 per cent. The two-year overall survival rate ranged from 89.9 per cent to 93 per cent. Only one of these four phase II trials reported a five-year overall survival rate (of 82.1 per cent).

In a retrospective propensity score analysis, Xia *et al.*[16] compared 96 patients who received concurrent cisplatin chemoradiotherapy plus cetuximab against 3126 patients who had received concurrent chemoradiotherapy alone. The median follow-up period was 5.17 years for the concurrent chemoradiotherapy plus cetuximab group and 5.24 years for the concurrent chemoradiotherapy group; there was a statistically significant difference in 5-year distant metastasis-free survival. The locoregional relapse-free survival, disease-free survival and overall survival rates were similar. A subgroup analysis showed a significant distant metastasis-free survival benefit with concurrent chemoradiotherapy plus cetuximab in patients with nodal N_{2-3} stage disease, compared with N_{2-3} patients receiving concurrent chemoradiotherapy alone (87.9 per cent *vs* 66.2 per cent, respectively; $p = 0.045$). Grade 3–4 mucositis was not significantly more common in the concurrent chemoradiotherapy plus cetuximab group (47.9 per cent *vs* 37.5 per cent; $p = 0.479$), but grade 3–4 skin rash was (16.7 per cent *vs* 0 per cent; $p < 0.0001$).[16]

In another retrospective study, by You *et al.*,[17] a propensity score-matched comparative analysis was carried out in patients with stage II–IVB NPC. The patients were treated with cisplatin-based chemoradiotherapy alone, or chemoradiotherapy in combination with biotherapy, either cetuximab or nimotuzumab. The survival outcomes appeared superior in the cetuximab/nimotuzumab group (three-year disease-free survival rate of 93.5 per cent *vs* 86.9 per cent ($p = 0.028$); three-year distant metastasis-free survival rate of 94.6 per cent *vs* 89.3 per cent ($p = 0.03$); and three-year overall survival rate of 96.6 per cent *vs* 92.9 per cent ($p = 0.015$)), but the treatment was associated with higher rates of grade 3 skin rash and grade 3–4 mucositis.[17]

In a recently published case–control retrospective study by Li *et al.*,[13] which compared the addition of cetuximab to chemoradiotherapy, there was no significant difference in five-

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Table 1. Cetuximab combined with chemoradiotherapy for locally advanced NPC

Study (year)	Study type	Patient population	Systemic therapies	Radiotherapy	Toxicities	Outcome	Additional comments
Feng *et al.*[9] (2014)	Phase II trial	*n* = 28. Cetuximab + concurrent cisplatin & RT in locoregionally advanced NPC. $T_{3-4}N_{0-4}M_0$ or $T_{0-4}N_{2-3}M_0$ (i.e. stage III–IVB). PS0–1	Cetuximab (standard dose*) on weekly basis for 7 wks + cisplatin 80 mg/m^2 on a 3-weekly basis with RT. Some patients had concurrent chemotherapy &/or 3 cycles of neoadjuvant cisplatin & fluorouracil	66–70+ Gy to primary tumour & 60–66 Gy to involved neck area in 2.0–2.27 Gy per fraction	Grade 3–4 mucositis = 71.4%. Grade 3 dysphagia = 57.1%. Grade 3 RT-related dermatitis = 25%. 3 patients (14.3%) had grade 3 & 1 patient (3.6%) had grade 4 cetuximab-related acneiform rashes	Primary tumour (*n* = 28): complete response = 89%, partial response = 11%. At a median f/u of 33.4 mth (95% CI = 29.2–38.1), 2-y PFS rate was 89.3% (95% CI = 76.4–98.1)	In 3 patients with partial response, biopsy confirmed persistent disease. Complete response was achieved in all 3 patients with salvage stereotactic RT
Zhang *et al.*[10] (2016)	Phase II trial	*n* = 43. Concurrent tomotherapy + cetuximab followed by adjuvant chemotherapy with cisplatin & docetaxel for locally advanced NPC. Stage III–IVB. PS0–1	Concurrent RT with cetuximab (standard dose*), followed by 4 cycles of chemotherapy (docetaxel (70 mg/m^2 on day 1) & cisplatin (40 mg/m^2 on days 1 & 2, every 3 wks). Cetuximab started on day 1 of RT rather than 1 wk earlier	70–74 Gy to gross tumour volume, 60–62.7 Gy to planning target volume 1, & 52–56 Gy to planning target volume 2, in 33 fractions	Grade 3 mucositis = 81.4%. RT-related dermatitis = 7.0%. Grade 3 osteonecrosis at 18 mth = 2.3%	Primary tumour: complete response = 95.3%, partial response = 4.7%. Nodal disease: complete response = 97.6%, partial response = 2.4%. With median f/u of 48 mth, 3-y locoregional failure-free, distant failure-free, PFS & OS rates were 92.7%, 85.6%, 72.0% & 85.7%, respectively. 2-y OS rate = 93%	100% of patients received all 7 cycles of cetuximab (only 1 patient received reduced dose). 42 patients (93%) completed all 4 cycles of adjuvant chemotherapy
Chen *et al.*[11] (2015)	Phase II trial	*n* = 100. Cetuximab combined with IMRT + concurrent cisplatin for locoregionally advanced NPC. Stage III–IVB	Cisplatin & cetuximab were given concurrently	66–75.9 Gy in 30–33 fractions with IMRT	2 patients with grade 4 mucositis. Late toxicity: dry mouth = 74%; hearing loss = 57%; trismus = 12%; RT-induced encephalopathy = 10%	Median f/u of 4.9 y. 5-y OS rate = 82.1%, DFS rate = 69%, RFS rate = 74.9%, DMFS rate = 75.2%	Overall, well-tolerated. Encouraging survival rates at 5-y, with no significant difference among different clinical stages
Wu *et al.*[12] (2018)	A 1:2 propensity score-matched analysis	After matching, 150 CRT patients & 75 CRT + cetuximab patients were analysed	Standard dose of cetuximab*. Concurrent chemotherapy regimens included docetaxel (70 mg/m^2 on day 1) with cisplatin (60 mg/m^2 on days 1–3) (TP regimen), or 3-weekly cisplatin (80 mg/m^2 on days 1–3) / nedaplatin (80 mg/m^2 on days 2–4)	66–75 Gy at 2.10–2.25 Gy per fraction to primary gross tumour, 64–72 Gy per 28–33 fractions to involved lymph nodes, 60–62 Gy per 28–31 fractions to high-risk clinical target, & 50–52 Gy per 25–30 fractions to low-risk clinical target	Grade 3–4 RT-related dermatitis & oral mucositis higher in CRT + cetuximab patients (21.3% *vs* 1.3% ($p < 0.001$), & 66.7% *vs* 10% ($p < 0.001$)). No difference in late toxicities	Improved 3-y PFS rate in CRT + cetuximab arm (83.7% *vs* 71.9%; $p = 0.036$), but not OS rate (91.4% *vs* 85.4%; $p = 0.117$). In subgroup analysis, in $T_4 \pm N_3$ patients, CRT + cetuximab significantly prolonged 3-y PFS rate (81.0% *vs* 61.4%; $p = 0.022$) & 3-y OS rate (88.0% *vs* 77.9%; $p = 0.086$)	Patients with T_3 &/or N_3 disease may get benefit from addition of cetuximab to CRT; however, it would be at increased risk of acute moderate to severe toxicities
Li *et al.*[13] (2017)	Case–control study of concurrent CRT with or without cetuximab in stage II–IVB NPC	62 concurrent CRT with cetuximab patients, & 124 concurrent CRT without cetuximab patients	All patients treated with cisplatin-based CRT (3-weekly or weekly). Standard doses of cetuximab* were used	2D-CRT: 70–76 Gy to primary tumour, 62–66 Gy to involved neck areas & 50 Gy to uninvolved areas. IMRT: 68–72 Gy (median, 70 Gy) at 2.12–2.24 Gy per fraction	Grade 3–4 mucositis: 51.6% with cetuximab *vs* 23.4% without cetuximab ($p < 0.001$). Rate of 10% weight loss: 66.1% with cetuximab *vs* 50.8% without cetuximab ($p = 0.47$). No significant difference in other toxicity rates	No significant difference. 5-y OS rate: 89.7% with cetuximab, 90.7% without cetuximab ($p = 0.386$). 3-y PFS rate: 83.9% with cetuximab *vs* 88.7% without cetuximab ($p = 0.115$)	Addition of cetuximab to concurrent CRT did not benefit survival, but exacerbated acute mucositis & acneiform rash
He *et al.*[14] (2013)	Prospective	*n* = 21. Cetuximab with CRT following induction chemotherapy for	1 cycle of induction chemotherapy followed by CRT & weekly cetuximab.	Not specified	Grade 4 leukopenia = 33.4%. Grade 4 neutropenia = 14.3. Grade 4 thrombocytopenia =	Median f/u of 13 mth (range, 3–23 mth). Local, regional & distant control rates were	All 21 patients completed planned RT, 14 patients (67%)

(*Continued*)

Table 1. (*Continued.*)

Study (year)	Study type	Patient population	Systemic therapies	Radiotherapy	Toxicities	Outcome	Additional comments
		locoregionally advanced NPC. Stage III–IVB. PS0–2	Cetuximab started on day 1 of RT. 33% had adjuvant chemotherapy. Induction, adjuvant & concurrent treatment comprised paclitaxel (155 mg/m^2 on day 1) & nedaplatin (40 mg/m^2 total on days 2–4), in 28-day cycles		4.8%. Grade 4 acneiform rash = 4.8%	100, 100 & 95.2%, respectively	without treatment breaks, & 20 patients (95.2%) completed planned cetuximab therapy
Ma *et al.*[15] (2012)	Phase II trial	*n* = 30. Cetuximab + concurrent cisplatin & IMRT in locoregionally advanced NPC. Stage III–IVB. PS0–1. WHO type II–III NPC	Initial dose of cetuximab (400 mg/m^2) 7–10 days before receiving concurrent IMRT, weekly cisplatin (30 mg/m^2/wk) & cetuximab (250 mg/m^2/wk)	IMRT: 74 Gy, 70 Gy, 62 Gy & 56 Gy to gross tumour, planning target of primary tumour & enlarged lymph nodes, upper neck lymphatics, & lower neck lymphatics, respectively, all completed in 35 daily fractions	Grade 3–4 mucositis = 87%. Short-term NG feeding required = 33%. Grade 3 RT-related dermatitis = 20%. Grade 3 cetuximab-related acneiform rash = 10%	Complete response = 25, partial response = 4, progressive disease = 1, overall response rate = 96%. At a median f/u of 31.8 mth (95% CI = 26.2–32.1), 2-y PFS rate was 86.5% (95% CI = 74.3–98.8). 2-y OS rate = 89.9%	Before 2007, RT dose was 66 Gy in 33 fractions
Xia *et al.*[16] (2017)	Retrospective (propensity score analysis)	*n* = 96. Comparison of concurrent cisplatin CRT + cetuximab (*n* = 131) *vs* concurrent CRT alone (*n* = 3126). After propensity score-matched analysis, 96 patients in each group	Induction chemotherapy in 35 patients within each group. Cisplatin weekly (30–40 mg/m^2) or 3-weekly (80–100 mg/m^2). Cetuximab (standard dose*)	No information given	Grade 3–4 mucositis: 47.9% in concurrent CRT + cetuximab patients, & 37.5% in concurrent CRT patients ($p = 0.479$). Grade 3–4 skin rash: 16.7% in concurrent CRT + cetuximab patients, & 0% in concurrent CRT patients ($p < 0.0001$)	Median f/u: 5.17 y for concurrent CRT + cetuximab arm, & 5.24 y for concurrent CRT arm. For concurrent CRT + cetuximab arm compared with concurrent CRT arm, 5-y DMFS, OS, DFS & locoregional RFS rates were: 94.1% *vs* 87.3% ($p = 0.045$), 89.3% *vs* 87.2% ($p = 0.920$), 83.4% *vs* 80.5% ($p = 0.839$), & 92.5% *vs* 93.2% ($p = 0.318$)	In concurrent CRT + cetuximab group, DMFS was improved, but with no improvement in OS. Effect was more marked among patients with advanced nodal stage disease
You *et al.*[17] (2017)	Retrospective propensity score analysis	*n* = 102 (concurrent CRT + cetuximab). Analysis between concurrent CRT (*n* = 689), *vs* concurrent CRT + anti-EGFR targeted treatment, cetuximab or nimotuzumab (*n* = 189)	Concurrent CRT (3 cycles of 100 mg/m^2 cisplatin every 3 wks with IMRT)	Overall median RT dose was 70 Gy (IQR, 70–70), with median dose per fraction of 2.19 Gy (IQR, 2.12–2.26)	Grade 3–4 haematological toxicities: 19.6% in cetuximab + concurrent CRT arm, 21.8% in nimotuzumab + concurrent CRT arm, & 19.4% in cisplatin ('CDDP') arm (all $p > 0.05$). Grade 3 skin rash: 42.2% in cetuximab arm, 5.7% in nimotuzumab arm, & 4.1% in concurrent CRT arm. Grade 3–4 mucositis: 52.9% in cetuximab arm, 32.1% in nimotuzumab arm, & 32.7% in concurrent CRT arm	Better outcomes in cetuximab/ nimotuzumab group (3-y DFS rate = 93.5% *vs* 86.9% ($p = 0.028$), 3-y DMFS rate = 94.6% *vs* 89.3% ($p = 0.03$) & 3-y OS rate = 96.6% *vs* 92.9% ($p = 0.015$)). Lower risk of progression (HR for DFS = 0.57, 95% CI = 0.35–0.94; $p = 0.028$), low risk of metastasis (HR = 0.52, 95% CI = 0.29–0.94; $p = 0.030$), & low risk of death (HR = 0.40, 95% CI = 0.19–0.84; $p = 0.015$) in cetuximab / nimotuzumab group	1-, 2- & 3-y respective OS rates were 98.9%, 97.2% & 96.6% in cetuximab/ nimotuzumab + concurrent CRT arm, & 98.1%, 95.5% & 92.9% in concurrent CRT arm

*Standard dose of cetuximab: initial dose of 400 mg/m^2 followed by weekly doses of 250 mg/m^2. NPC = nasopharyngeal carcinoma; RT = radiotherapy; TNM = tumour–node–metastasis; PS = performance status; wk = week; f/u = follow up; mth = months; CI = confidence interval; y = years; PFS = progression-free survival; OS = overall survival; IMRT = intensity-modulated radiotherapy; DFS = disease-free survival; RFS = relapse-free survival; DMFS = distant metastasis-free survival; CRT = chemoradiotherapy; TP = docetaxel plus cisplatin (without 5-fluorouracil); 2D = two-dimensional; WHO = World Health Organization; NG = nasogastric; EGFR = epidermal growth factor receptor; IQR = interquartile range; HR = hazard ratio

Table 2. Cetuximab plus RT compared with chemoradiotherapy for locally advanced NPC

Study (year)	Study type	Patient population	Systemic therapies	Radiotherapy	Toxicities	Outcome	Additional comments
Zhu *et al.*[18] (2013)	Phase II randomised trial	$n = 44$. Induction chemotherapy, followed by concurrent CRT or concurrent cetuximab-RT (ERT) in locally advanced NPC. Stage III–IVB	2 cycles of induction chemotherapy (cisplatin 80 mg/m^2 + docetaxel 75 mg/m^2 on day 1), then either CRT with cisplatin (30 mg/m^2 weekly) or ERT (RT with cetuximab (standard dose*))	IMRT: 66–70.4 Gy in 30–32 fractions	During induction chemotherapy: grade 3 neutropenia = 81.8%, grade 4 neutropenia = 9.1%. In ERT arm: grade 3 mucositis = 100%, grade 4 mucositis = 85.7%. In CRT arm: grade 3 mucositis = 50%, grade 4 mucositis = 8.7%	After induction chemotherapy: response = 95% (1 complete response, 41 partial response & 2 stable disease). After median f/u of 21.4 mth, 2-y PFS rates were 90.9% & 82.1% ($p > 0.05$) in ERT arm & CRT arm respectively	All patients completed 2 cycles of induction chemotherapy. In ERT: 97% had all 7 cycles of cetuximab. In CRT: 17.4% had all 6 cycles of cisplatin, 52.2% had 5 cycles, 21.7% had 4 cycles & 8.7% had 3 cycles. 95.2% completed all 7 cycles of cetuximab
Wu *et al.*[19] (2016)	Retrospective, matched case–control study	$n = 112$ (56 in each group). Patients with previously untreated, locally advanced NPC were matched into pairs: concurrent cetuximab-based BRT or cisplatin-based CRT. Stage II–IVB. PS0–1. 4 patients aged <20 y, including 1 aged 15 y	2 cycles of TPF induction regimen (paclitaxel 150–175 mg/m^2 on day 1+, cisplatin 25 mg/m^2 on days 1–3+, & fluorouracil 600 mg/m^2 through days 1–5) every 21 days. In BRT arm: cetuximab (standard dose*) during RT. In CRT arm: 3 cycles of 25 mg/m^2 cisplatin on days 1–3, every 3 wks	IMRT with variable 2.12–2.24 Gy fractions per day & 5 days per wk, up to a total of 70–74 Gy in 33 fractions	CRT patients had greater grade 3–4 haematology toxicities (all statistically significant), & more severe vomiting ($p = 0.0001$). BRT patients had more severe acneiform skin reactions ($p = 0.0001$) & severe mucositis ($p = 0.0001$)	Median f/u time was 55.4 mth (range, 33–73 mth) in BRT arm & 56.2 mth (range, 36–70 mth) in CRT arm. Differences in OS were not statistically significant, with 5-y actuarial rates of 79.5% for BRT & 79.3% for CRT (log-rank $p = 0.797$), & 3-y survival rates of 92.9% & 92.8%. Median OS of 66.8 mth for BRT & 67.3 mth for CRT patients	BRT was not inferior to traditional CRT. In BRT arm, grade 3–4 rash & mucositis was associated with improved survival on univariate analysis
Xu *et al.*[20] (2015)	Randomised phase II trial	$n = 44$. Induction chemotherapy, followed by concomitant cisplatin CRT ($n = 23$) or cetuximab-RT (ERT, $n = 21$)	2 cycles of induction chemotherapy (docetaxel 75 mg/m^2 on day 1+ cisplatin 80 mg/m^2 on day 1), followed by weekly cisplatin (30 mg/m^2) or weekly cetuximab (standard dose*) along with RT	IMRT: 66–70.4 Gy	Grade 3–4 mucositis: 47.8% in CRT arm & 80.9% in ERT arm ($p = 0.023$). Grade 3–4 acneiform rash: 0% in CRT arm *vs* 33.3% in ERT arm ($p = 0.009$). Grade 3–4 dysphagia: 13% in CRT arm *vs* 47.6% in ERT arm ($p = 0.012$)	All patients except 1 in ERT arm achieved complete response 3 mth after treatment ($p = 0.47$). 3-y DFS rates of 78.3% in CRT arm & 85.7% in ERT arm ($p = 0.547$). No difference in 3-y OS rates (95.7% *vs* 100%; $p = 0.619$), 3-y MFS rates (78.3% *vs* 85.7%; $p = 0.508$) or 3-y RFS rates (95.7% *vs* 95.2%; $p = 0.961$) in 2 treatment arms	Study was closed ahead of schedule, because of unexpectedly high rates of grade 3–4 mucositis in ERT arm

*Standard dose of cetuximab: initial dose of 400 mg/m^2 followed by weekly doses of 250 mg/m^2. RT = radiotherapy; NPC = nasopharyngeal carcinoma; CRT = chemoradiotherapy; ERT = Erbitux® plus radiotherapy; IMRT = intensity-modulated radiotherapy; f/u = follow up; mth = months; y = years; PFS = progression-free survival; BRT = bio-radiotherapy; PS = performance status; TPF = docetaxel, cisplatin and 5-fluorouracil; wk = week; OS = overall survival; DFS = disease-free survival; MFS = metastasis-free survival; RFS = relapse-free survival

Table 3. Cetuximab with RT, with or without chemotherapy, for locally advanced NPC

Study (year)	Study type	Patient population	Systemic therapies	Radiotherapy	Toxicities	Outcome	Additional comments
Niu *et al.*[21] (2013)	Retrospective	*n* = 33. Cetuximab + IMRT with or without chemotherapy for locoregionally advanced NPC. Stage II–IVB. WHO type II/III NPC. (PS not stated)	Cetuximab (standard dose*). 90.9% of patients received various regimens of neoadjuvant, concurrent or adjuvant platinum-based chemotherapy. 64% had concurrent CRT, 54.5% had neoadjuvant, 18.2% had adjuvant	IMRT: doses of 66–70.4 Gy, 66 Gy, 60 Gy & 54 Gy were given to gross tumour volume, positive neck nodes, high-risk clinical target volume & low-risk clinical target volume, respectively	Grade 3 stomatitis = 69.7%, grade 4 stomatitis = 15.2%, grade 3 dermatitis = 18.2%, grade 3 acneiform rash = 39.4%. Temporal lobe necrosis was observed in 7 patients (21%)	Objective response = 100% (complete response = 87.9%) at 3 mth. At median f/u of 40 mth, 3-y PFS, DMFS & OS rates were 70.5% (95% CI = 54.0–87.0%), 83.6% (95% CI = 70.3–96.9%) & 90.9% (95% CI = 81.1–100.0%), respectively	Patients who received ≥7 cycles of cetuximab showed better 3-y PFS than those who received <7 cycles (79.1% *vs* 31.2%; $p = 0.050$)

*Standard dose of cetuximab: initial dose of 400 mg/m^2 followed by weekly doses of 250 mg/m^2. RT = radiotherapy; NPC = nasopharyngeal carcinoma; IMRT = intensity-modulated radiotherapy; WHO = World Health Organization; PS = performance status; CRT = chemoradiotherapy; mth = months; f/u = follow up; y = years; PFS = progression-free survival; DMFS = distant metastasis-free survival; OS = overall survival; CI = confidence interval

Table 4. Cetuximab with induction chemotherapy followed by RT for locally advanced NPC

Study (year)	Study type	Patient population	Systemic therapies	Radiotherapy	Toxicities	Outcome	Additional comments
Lin *et al.*[22] (2016)	Prospective	*n* = 42. Induction bio-chemotherapy followed by RT. Stage III–IV. 25 of 42 (59.5%) were PS0–1	Induction of chemotherapy weekly (cisplatin 60 mg/m^2 on day 1, 5-fluorouracil 2500 mg/m^2 + leucovorin 250 mg/m^2 on day 8) ± docetaxel 50 mg/m^2 or gemcitabine 1000 mg/m^2 on day 15, for 10–12 wks, & concurrent cetuximab (standard dose*)	Conventional (70 Gy in 35 fractions) or hyperfractionated (76.4 Gy in 64 fractions for T_4 tumour). RT delivered by IMRT technique	Grade 3–4 skin rash = 50%, all grades skin rash = 100%, all grades dry skin = 64.3%, all grades paronychia = 52.4%, all grades of hypomagnesemia = 28.6% (12 of 42). Grade 3–4 conventional toxicities were rare (11.9% leucopoenia, 9.5% anaemia, 2.4% thrombocytopenia & 2.4% mucositis)	Response after induction bio-chemotherapy: complete response = 50%, partial response = 50%. After median f/u of 24 mth, there was 1 local, 1 regional & 5 distant failures. 3-y local failure-free survival, neck failure-free survival, DMFS, PFS & OS rates were 96.6%, 96.0%, 87.4%, 79.9% & 92.1%, respectively	High pre-treatment plasma EBV DNA was associated with significantly lower PFS & DMFS ($p = 0.01$ & $p = 0.004$), but not OS ($p = 0.629$). Patients with detectable plasma EBV DNA after bio-chemotherapy had significantly lower OS, PFS & DMFS rates ($p = 0.029$, $p = 0.007$ & $p = 0.008$, respectively)

*Standard dose of cetuximab: initial dose of 400 mg/m^2 followed by weekly doses of 250 mg/m^2. RT = radiotherapy; NPC = nasopharyngeal carcinoma; PS = performance status; wk = week; IMRT = intensity-modulated radiotherapy; f/u = follow up; mth = months; y = years; DMFS = distant metastasis-free survival; PFS = progression-free survival; OS = overall survival; EBV = Epstein–Barr virus

Table 5. Cetuximab with induction chemotherapy followed by chemoradiotherapy, or induction chemotherapy followed by cetuximab and RT, for locally advanced NPC

Study (year)	Study type	Patient population	Systemic therapies	Radiotherapy	Toxicities	Outcome	Additional comments
Peng *et al.*[23] (2018)	Retrospective	149 patients in investigational arm: induction chemotherapy + cetuximab ($n = 56$) or nimotuzumab ($n = 93$) followed by CRT. 147 patients in control arm: induction chemotherapy followed by RT + cetuximab ($n = 25$) or nimotuzumab ($n = 122$)	Induction chemotherapy consisted of various combinations of docetaxel, cisplatin & fluorouracil. Concurrent chemotherapy was tri-weekly cisplatin (80–100 mg/m^2) or weekly cisplatin (30–40 mg/m^2). Standard dose of cetuximab*	66–72 Gy at 2.12–2.43 Gy per fraction to primary gross tumour, 64–70 Gy in 28–33 fractions to involved lymph nodes, 60–63 Gy in 28–33 fractions to high-risk clinical target volume & 54–56 Gy in 28–33 fractions to low-risk clinical target volume	In investigational arm, grade 3–4 skin reaction (15.4% *vs* 2%; $p < 0.001$) & mucositis (10.1% *vs* 3.4%; $p = 0.02$) were higher during induction phase, but less skin reaction & mucositis during RT phase	3-y DFS, OS, DMFS & locoregional RFS rates for investigational arm *vs* control arm were 84.3% *vs* 74.3% ($p = 0.027$), 94.0% *vs* 92.1% ($p = 0.673$), 88.0% *vs* 81.8% ($p = 0.147$), & 93.3% *vs* 88.0% ($p = 0.093$), respectively	No separate information (subgroup analysis) available regarding patients who received cetuximab rather than nimotuzumab

*Standard dose of cetuximab: initial dose of 400 mg/m^2 followed by weekly doses of 250 mg/m^2. RT = radiotherapy; NPC = nasopharyngeal carcinoma; CRT = chemoradiotherapy; y = years; DFS = disease-free survival; OS = overall survival; DMFS = distant metastasis-free survival; RFS = relapse-free survival

Table 6. Induction chemotherapy followed by bio-chemoradiotherapy for locally advanced, recurrent NPC

Study (year)	Study type	Patient population	Systemic therapies	Radiotherapy	Toxicities	Outcome	Additional comments
Ng *et al.*[24] (2018)	Phase II trial	$n = 33$. Induction chemotherapy, followed by bio-CRT with docetaxel & cetuximab	3 cycles of TPF chemotherapy, followed by weekly docetaxel & cetuximab (standard dose*) with RT	60 Gy	Temporal lobe necrosis in 8 cases. Grade ≥3 hearing loss, soft tissue necrosis, dysphagia & trismus in 30.8%, 15.4%, 11.5% & 19.2%, respectively	Complete response = 30.8%. 3-y PFS & OS rates were 35.7% & 63.8%, respectively	Overall, 5 patients died owing to acute (1 after cycle 1 TPF, & 1 after completion of bio-CRT) or late (2 epistaxis & 1 temporal lobe necrosis) treatment-related complications

*Standard dose of cetuximab: initial dose of 400 mg/m^2 followed by weekly doses of 250 mg/m^2. NPC = nasopharyngeal carcinoma; CRT = chemoradiotherapy; TPF = docetaxel, cisplatin and 5-fluorouracil; RT = radiotherapy; y = years; PFS = progression-free survival; OS = overall survival

Table 7. Cetuximab plus chemotherapy for recurrent and/or metastatic NPC

Study (year)	Study type	Patient population	Systemic therapies	Radiotherapy	Toxicities	Outcome	Additional comments
Chan *et al.*[25] (2005)	Phase II trial	*n* = 60. NPC patients with EGFR expression who had disease progression at or within 12 mth after termination of platinum-based chemotherapy for recurrent or metastatic disease. 7% were not of Chinese origin. PS0–2	Cetuximab (standard dose*). Carboplatin target area under curve of 5 every 3 wks, up to a maximum of 8 cycles	Not applicable	Serious treatment-related adverse events in 10%. Grade 3–4 toxicities occurred in 31 patients (51.7%). 2 of 60 (3.3%) had grade 3–4 acneiform rash	Partial response = 11.7%, stable disease = 48.3%, progressive disease = 38.3%, overall response rate = 11.7% (95% CI = 4.8–22.6). Median time to progression = 81 days. Median OS = 233 days. Median duration of response was 99 days (3.3 mth)	Median survival appeared longer in patients with grade 3–4 acne rash, but there were only 2 such patients. OS also seemed to be improved in males. Karnofsky PS ≥80; second-line *vs* later line; >90 days from previous chemotherapy
Kerboua *et al.*[26] (2015)	Phase II trial (single arm)	*n* = 54. Recurrent or metastatic undifferentiated NPC patients who had disease progression at or within 12 mth after termination of platinum-based chemotherapy	Cetuximab 400 mg/m^2, followed every 2 wks by doses of 500 mg/m^2 until progression or unacceptable toxicity. Cisplatin 70 mg/m^2 on day 1 every 3 wks, up to a maximum of 4 cycles	Not applicable	Grade 3 cutaneous toxicities occurred in 5 patients	Complete response = 8%, partial response = 20%, stable disease = 50%, progressive disease = 22%, overall response rate = 78%. Median time to progression = 19.5 mth (range, 3–25 mth). Median OS = 22 mth	

*Standard dose of cetuximab: initial dose of 400 mg/m^2 followed by weekly doses of 250 mg/m^2. NPC = nasopharyngeal carcinoma; EGFR = epidermal growth factor receptor; mth = months; PS = performance status; wk = week; CI = confidence interval; OS = overall survival

Table 8. Cetuximab plus chemoradiotherapy for recurrent and/or metastatic NPC

Study (year)	Study type	Patient population	Systemic therapies	Radiotherapy	Toxicities	Outcome	Additional comments
Lin *et al.*[27] (2016)	Prospective trial	43 in study group with chemotherapy-naive metastatic disease including initial metastases & first relapse metastases. 66 in control group, who received conventional CRT	Induction chemotherapy with docetaxel 75 mg/m^2, cisplatin 75 mg/m^2 & cetuximab 250 mg/m^2, on days 1, 8 & 15 (after loading dose of 400 mg/m^2), repeated every 3 wks up to a maximum of 6 cycles	IMRT (68–70 Gy) with concurrent cetuximab 250 mg/m^2 weekly for 6 cycles & cisplatin 75 mg/m^2 per 3 wks for 2 cycles, & maintenance capecitabine + celecoxib for 3 y	5 patients (11.6%) had grade 3 cetuximab-related acneiform rash. Occurrence of other most common toxicities were similar between the 2 groups	Study group: objective response = 79.1%, complete response = 34.9%. Control group: objective response = 47%, complete response = 3%. With a median f/u of 60 mth, 5-y OS & PFS rates were 28.9% & 16.7% in study group, & 10.9% & 0% in control group, respectively	In study group, objective & complete response rates were higher in initial metastases subgroup than in relapse metastases subgroup (94.1% *vs* 69.2%, & 52.9% *vs* 23.1%, respectively). At >36 mth, 10 patients were still alive, with DFS of 46 to 92+ mth
Xu *et al.*[28] (2016)	Retrospective	*n* = 30. Recurrent &/or metastatic NPC patients treated with comprehensive therapy including cetuximab. PS0–2 (96.2% were PS0–1). Patients had previously undergone concurrent CRT ± neoadjuvant chemotherapy ± second-line TPF	Chemotherapy regimens included TP or TPF (docetaxel 60–75 mg/m^2 on day 1 + 'DDP' (cisplatin) 25 mg/m^2 on days 1–3 ± 5-fluorouracil 500 mg/m^2/day with 120-hour infusion), 'GP' (gemcitabine 1.0 g/m^2 on day 1 & day 8, + DDP 25 mg/m^2 on days 1–3), & 'PC' (paclitaxel 60 mg/m^2/wk on day 1 + carboplatin target area under curve of 2 per wk on day 1)	In recurrent disease, IMRT was delivered in 14 patients, with a median dose of 60 Gy (54–66 Gy)	Grade 3–4 acne-like rash = 20%, grade 3–4 oral mucositis = 21.4%, grade 3–4, grade 3–4 dry skin = 6.7%	Complete response = 3 (10%), partial response = 18 (60%), stable disease = 7 (23%), progressive disease = 2 (7%), objective response rate = 70%. Median OS rate, time to progression & 2-y OS rate were 23.6%, 12.2 mth & 53.3%, respectively	Authors concluded that addition of cetuximab to CRT for recurrent &/or metastatic NPC was effective, with tolerable toxicities

NPC = nasopharyngeal carcinoma; CRT = chemoradiotherapy; wk = week; IMRT = intensity-modulated radiotherapy; y = years; f/u = follow up; OS = overall survival; PFS = progression-free survival; mth = months; DFS = disease-free survival; PS = performance status; TPF = docetaxel, cisplatin and 5-fluorouracil; TP = docetaxel plus cisplatin (without 5-fluorouracil)

year overall survival rates (89.7 per cent with cetuximab and 90.7 per cent without cetuximab; $p = 0.386$). However, there was a significant difference in grade 3 and 4 toxicities with the addition of cetuximab (grade 3–4 mucositis in 51.6 per cent of patients treated with cetuximab and 23.4 per cent in the group without cetuximab; $p < 0.001$).

Induction chemotherapy, followed by cetuximab plus radiotherapy or chemoradiotherapy

In a phase II trial conducted by Xu *et al.*,[20] two cycles of induction chemotherapy (cisplatin and docetaxel) followed by either cisplatin-based chemoradiotherapy or cetuximab-RT (Erbitux® plus RT) were evaluated. Although there were no significant differences in the outcome, the study was closed ahead of schedule because of the higher rates of grade 3–4 mucositis in the Erbitux plus RT arm (80.9 per cent in the Erbitux plus RT arm, *vs* 47.8 per cent in the chemoradiotherapy arm; $p = 0.023$). The rate of grade 3–4 acneiform rash was 33.3 per cent in the Erbitux plus RT arm, versus 0 per cent in the chemoradiotherapy arm ($p = 0.009$).[20]

In a retrospective, matched case–control study that compared the safety and efficacy of concurrent cetuximab-based bio-radiotherapy and cisplatin-based chemoradiotherapy in the treatment of locally advanced NPC, patients received two cycles of docetaxel, cisplatin and 5-fluorouracil ('TPF') induction chemotherapy, followed by either bio-radiotherapy or chemoradiotherapy.[19] Survival outcomes were similar (five-year overall survival rate of 79.5 per cent for bio-radiotherapy and 79.3 per cent for chemoradiotherapy; $p = 0.797$). There was a higher incidence of grade 3–4 haematological toxicity and severe vomiting with chemoradiotherapy. The bio-radiotherapy patients experienced more severe rashes and mucositis.[19]

Cetuximab with radiotherapy, with or without chemotherapy

In a retrospective study, Niu *et al.*[21] evaluated the safety and efficacy of cetuximab plus intensity-modulated RT, with or without chemotherapy, for locally advanced NPC ($n = 33$). The majority of patients (91 per cent) received platinum-based neoadjuvant, concurrent or adjuvant chemotherapy. The three-year progression-free survival and overall survival rates were 70.5 per cent and 90.9 per cent, respectively. For the cetuximab plus intensity-modulated RT group, the grade 3–4 stomatitis rate was 84.9 per cent. Temporal lobe necrosis was observed in seven patients (21 per cent). The authors concluded that cetuximab plus intensity-modulated RT, with or without chemotherapy, for locally advanced NPC was effective and tolerable.[21]

Cetuximab with induction chemotherapy, followed by radiotherapy alone

At the European Society for Therapeutic Radiology and Oncology annual meeting in 2016, Lin *et al.*[22] presented results from a case series of patients treated with an induction bio-chemotherapy regimen (cisplatin, 5-fluorouracil and leucovorin, with or without docetaxel or gemcitabine, and weekly cetuximab) followed by RT (70–76.4 Gy) in 42 patients with stage III/IV NPC. Each patient received a mean of 11 weeks of cetuximab treatment. After induction bio-chemotherapy, all patients responded (50 per cent complete response and 50 per cent partial response). The three-year progression-free survival and overall survival rates were 79.9 per cent and 92.1 per cent respectively. The rates of grade 3–4 toxicities were: skin rash, 50 per cent; leucopoenia, 11.9 per cent; anaemia, 9.5 per cent; thrombocytopenia, 2.4 per cent; and mucositis, 2.4 per cent. Basal plasma Epstein–Barr virus DNA levels were the most important prognostic factor.[22]

Cetuximab with induction chemotherapy followed by chemoradiotherapy, or induction chemotherapy followed by cetuximab and radiotherapy

In a recently published retrospective analysis by Peng *et al.*,[23] a cohort of patients who received cetuximab or nimotuzumab in combination with induction chemotherapy followed by chemoradiotherapy (investigational arm) was compared against those who received induction chemotherapy followed by RT plus cetuximab or nimotuzumab (control arm). Three-year overall survival rates were similar (94 per cent *vs* 92.1 per cent; $p = 0.673$); however, the three-year disease-free survival rate was higher in the investigational arm (84.3 per cent *vs* 74.3 per cent; $p = 0.027$). In the investigational arm, the rates of grade 3–4 skin reaction (15.4 per cent *vs* 2 per cent; $p < 0.001$) and grade 3–4 mucositis (10.1 per cent *vs* 3.4 per cent; $p = 0.02$) were higher during the induction phase.[23]

Recurrent and/or metastatic nasopharyngeal carcinoma

Induction chemotherapy followed by bio-chemoradiotherapy

A phase II trial, published by Ng *et al.* in 2018,[24] evaluated three cycles of docetaxel, cisplatin and 5-fluorouracil, followed by weekly docetaxel and cetuximab concurrently with RT, in locally advanced recurrent NPC. Although complete response was achieved in 30.8 per cent of cases, and three-year progression-free and overall survival rates were 35.7 per cent and 63.8 per cent respectively, the regimen was very toxic (temporal lobe necrosis, 24 per cent; grade 3 or greater hearing loss, 30.8 per cent; grade 3 or greater trismus, 19.2 per cent; and grade 3 or greater soft tissue necrosis, 15.4 per cent). Overall, 5 out of 33 patients died owing to treatment-related complications.[24]

Chemotherapy plus cetuximab

In two phase II trials, the toxicity and efficacy of cetuximab in combination with carboplatin[25] or cisplatin[26] in recurrent and/or metastatic NPC patients, in whom disease had progressed at or within 12 months following completion of platinum-based chemotherapy, were evaluated. The overall response rates (complete or partial response, and stable disease) were 60 per cent with carboplatin and 78 per cent with cisplatin. Median overall survival was 7.7 months with carboplatin and 22 months with cisplatin. The toxicity profile in both studies was acceptable. The authors of both studies concluded that the regimens were clinically effective, with acceptable safety profiles.[25,26]

Chemoradiotherapy plus cetuximab

As presented in a poster at the European Society of Medical Oncology annual meeting in 2016, Lin *et al.*[27] explored the efficacy of first-line cetuximab plus platinum and taxane as induction chemotherapy followed by chemoradiotherapy and a subsequent three-year maintenance treatment regime for patients with chemotherapy-naive distant metastatic NPC. In the study group, 43 patients (17 with newly diagnosed initial metastases, and 26 with first relapse metastases) received induction chemotherapy consisting of cetuximab, cisplatin and docetaxel followed by chemoradiotherapy concurrently with cetuximab and cisplatin, followed by maintenance capecitabine and celecoxib for three years. In the control group,

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patients received platinum-based induction chemotherapy followed by conventional chemoradiotherapy ($n = 66$). After induction chemotherapy, the objective response and complete response rates were 79.1 per cent and 34.9 per cent for the study group, and 47 per cent and 3 per cent for the control group, respectively. With a median follow up of 60 months, 5-year overall survival and progression-free survival rates were 28.9 per cent and 16.7 per cent in the study group, and 10.9 per cent and 0 per cent in the control group, respectively. The rate of grade 3 cetuximab-related acneiform rash was 11.6 per cent. The authors concluded that 'the cetuximab-containing induction and consolidation chemoradiotherapy patients with chemotherapy-naive metastatic NPC resulted in excellent long-term disease-free survival and safety, indicating that metastatic NPC is potentially curable, especially in patients with IM [initial metastases]'.[27]

In a similar retrospective study, Xu *et al.*[28] reported the efficacy and safety of cetuximab plus chemotherapy, using three different regimens (i.e. docetaxel and cisplatin plus 5-fluorouracil; gemcitabine plus cisplatin; or paclitaxel plus carboplatin). Each of these chemotherapy and cetuximab regimens was added to intensity-modulated RT in the treatment of 30 patients with recurrent and/or metastatic NPC. Twenty-one patients (70 per cent) achieved a response (3 complete responses and 18 partial responses). The median survival time was 23.6 months and the 2-year overall survival rate was 53.3 per cent. The toxicity profile was acceptable according to the authors.[28]

Ongoing study – cetuximab plus chemotherapy or chemoradiotherapy

A randomised, controlled, multicentre, phase III trial comparing cetuximab, cisplatin and docetaxel induction chemotherapy followed by concurrent chemoradiotherapy with cisplatin plus docetaxel in untreated metastatic NPC is currently ongoing. The estimated date of completion for this study (trial identifier: NCT02633176) is January 2023.

Discussion

The cornerstone of treatment for locoregionally advanced nasopharyngeal carcinoma (NPC) is RT. Additional chemotherapy given in the concurrent setting is associated with improved outcomes, but at the expense of increased toxicity, especially radiation-induced mucositis. The meta-analysis by Blanchard *et al.*[29] confirmed that the addition of concomitant chemotherapy to RT significantly improves overall survival in NPC (hazard ratio = 0.79, 95 per cent confidence interval (CI) = 0.73–0.86 ($p < 0.0001$); absolute benefit at five years = 6.3 per cent, 95 per cent CI = 3.5–9.1). The addition of chemotherapy, either adjuvant or induction, alongside concomitant chemoradiotherapy is gaining popularity, although the most effective sequence has not been determined. In an individual patient data network meta-analysis, the addition of adjuvant chemotherapy to concomitant chemoradiotherapy achieved the highest survival outcome,[30] while another network meta-analysis showed that induction chemotherapy followed by concurrent chemoradiotherapy was the most effective regimen.[2]

Concurrent cetuximab with RT has been widely used in the treatment of head and neck cancer;[7] however, in NPC, level 1 evidence is lacking. In the management of primary NPC, there has only been one phase II trial comparing cetuximab and RT versus cisplatin and RT, and both these regimens were given after initial induction chemotherapy with docetaxel and cisplatin.[20] The study closed early because of the much higher incidence of mucositis in the cetuximab arm (80.9 per cent) compared with the cisplatin arm (47.8 per cent). Other morbidities were also higher in the cetuximab group (Table 2). This study comprised only 44 patients: 23 in the cisplatin-RT arm and 21 in the cetuximab-RT arm. The final sample size was therefore too low to draw any firm conclusions regarding survival outcomes.[20]

Given the heterogeneity of the studies presented in this narrative review, and the inherent selection bias evident in the non-randomised trials, meta-analysis of the results was not appropriate. While some series have presented encouraging survival outcomes, no single trial has offered level 1 evidence or irrefutable evidence to demonstrate the clinical effectiveness of adding cetuximab to standard chemoradiotherapy. However, there appears to be a trend towards greater toxicity (especially in regard to skin reactions and mucositis) reported in those patient groups treated with additional cetuximab compared to standard chemoradiotherapy regimens. There is also some evidence that the addition of cetuximab to RT following induction chemotherapy may lead to unacceptably high toxicity.[19,20]

Lin *et al.*[22] claimed that induction bio-chemotherapy with cetuximab, followed by intensity-modulated RT, was a 'highly effective protocol'. However, the authors of the current review feel that the results of Lin and colleagues' study should be interpreted with caution. The results have not yet been published in full, and there were a limited number of patients in the study. In addition, a recent randomised phase II European Organisation for Research and Treatment of Cancer ('EORTC') trial, of docetaxel, cisplatin and 5-fluorouracil plus cetuximab induction chemotherapy followed by bio-chemoradiotherapy, with weekly cetuximab plus weekly cisplatin or carboplatin, in head and neck squamous cell carcinoma patients, showed unacceptable complications that led to the study closing prematurely.[31]

A series of retrospective studies compared cetuximab use in NPC against matched historic chemoradiotherapy data.[16,17,19,21] These showed a potential benefit with the addition of cetuximab, either in general[17,19,21] or in some subgroups.[16] These retrospective studies, which comprised a small number of patients, can also be criticised for inappropriate subset analyses when the studies were originally not set up to answer such questions. All the studies showed increased morbidity in patients who received cetuximab, including one study with a 21 per cent incidence of temporal lobe necrosis.[21] A wide range of historic treatments, including neoadjuvant, concurrent and adjuvant chemotherapy, was used in these comparative studies, and so the benefit of using cetuximab alone or in combination with platinum-based chemotherapy is difficult to determine.

Evidence for the use of cetuximab in the management of recurrent or metastatic NPC is limited by the small number of studies, all of which contain relatively small numbers of patients. The use of cetuximab in combination with chemotherapy was tested in two phase II trials (the total number of patients in these 2 trials was only 114).[25,26] The authors of both studies concluded that the regimens were clinically effective, with acceptable safety profiles. However, there has been criticism of these findings. Both studies enrolled patients with progressive disease within 12 months of completing platinum-based chemotherapy, which means they are likely to have included patients who were partially cisplatin-sensitive. Indeed, the authors themselves found that prolonged overall survival was dependent on the

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interval (over 90 days *vs* under 90 days) between completing platinum-based previous chemotherapy and platinum-based second-line chemotherapy.[25] Therefore, the use of cetuximab would be better explored in combination with other chemotherapeutic agents in a population of patients who are strictly defined as platinum-resistant.[32]

The results of a small study of cetuximab with induction chemotherapy, followed by chemoradiotherapy with concomitant cisplatin and cetuximab, and then followed by maintenance capecitabine and celecoxib, in chemotherapy-naive distant metastatic NPC patients, seem promising.[27] However, this has only been presented as an abstract (no information is available regarding the inclusion criterion for patients enrolled in the controlled group), and a high rate of 'cure' in metastatic disease seems unlikely. For such intense treatment regimes, good patient selection is key (i.e. oligometastatic disease in fit patients). However, the very small numbers of patients in the subgroups do not allow firm deductions to be made.[27]

In the locoregional setting, there is consistently no significant benefit from the addition of cetuximab, and it comes with an increase in toxicity. However, the use of cetuximab in the metastatic or locally recurrent situation may have more promise, either for more effective palliation alongside other chemotherapy regimens, or as part of an induction regimen prior to salvage treatment.

This review has drawn together published studies focusing on NPC that have used cetuximab in combination with standard, evidence-based treatments. It shows that there has been great interest and endeavour in trying to improve the outcome for NPC patients, and a wide variety of treatment strategies have been utilised. The reason why cetuximab does not seem to add benefit to the treatment of locoregional disease may be because the outcome is already very good for the majority of patients, and the side effects from conventional chemoradiotherapy, although tolerable, are significant. Therefore, if future trials focus on NPC patients with poorer prognosis, they are likely to produce more convincing evidence for a beneficial role of cetuximab.

Conclusion

At this point in time, there is no evidence supporting the addition of cetuximab to standard management protocols for nasopharyngeal carcinoma. There is more promise for its use in the metastatic or locally recurrent setting, and this could be a focus for future investigation.

Competing interests. None declared

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