

Recent results of cetuximab use in the treatment of squamous cell carcinoma of the head and neck

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Abstract: Cetuximab is a chimeric monoclonal antibody that targets the epidermal growth factor receptor. The role of cetuximab is paramount in several subsets of head and neck cancer. In particular, the EXTREME study has indicated cetuximab as the only drug to improve survival when associated with cisplatin and 5-fluorouracil in patients with recurrent/metastatic disease. Furthermore, cetuximab, both alone and in combination with cisplatin, is active in patients with recurrent/metastatic disease who have failed prior platinum-based chemotherapy. Cetuximab, given in association with radiation therapy, is a treatment of choice in first-line therapy of patients with locally advanced inoperable disease. In the same setting, the role of induction chemotherapy has gained considerable interest over the last few years and a number of efforts are being pursued to optimally integrate induction chemotherapy with radiation therapy plus cetuximab. The combination of cetuximab and other targeted therapies is among the most promising new perspectives for patients with head and neck cancer.

Keywords: cetuximab, head and neck cancer, locally advanced, recurrent/metastatic

Introduction

Epithelial growth factor receptor (EGFR) is a member of the ErbB family of receptors which are composed of an extracellular ligand-binding domain, a hydrophobic transmembrane segment and an intracellular tyrosine kinases domain. After ligand binding, homodimeric or heterodimeric complexes are formed which activate in turn the tyrosine kinase domain and downstream effectors.¹ Squamous cell carcinoma of the head and neck (SCCHN) represents a suitable tumor in which anti-EGFR therapy can be explored due to nearly ubiquitous EGFR expression and its prognostic value. EGFR plays a critical role in SCCHN growth, invasion, metastasis and angiogenesis,² and the mean EGFR levels in tumors are considerably higher than in normal tissue.³ High EGFR copy number detected by fluorescence *in situ* hybridization (FISH) has been shown to be a poor prognostic indicator.⁴ A similar study,⁵ including 134 patients with diagnosis of SCCHN, demonstrated that aberrant EGFR copy numbers, evaluated by quantitative real-time polymerase chain reaction (Q RT-PCR), is also associated with a poor clinical outcome. In both of the studies, the increased EGFR copy number does not correlate with the protein expression levels. Recently, the role of any EGFR gene polymorphism was explored in several human epithelial neoplasms including SCCHN. These polymorphisms [nucleotidic substitution G/A in the 497 codon of the exon 13 (R497K); 216G/T substitution in SP1 region of the promoter; CA dinucleotidic repetitions in the intron 1] seem to increase gene EGFR expression and correlate with a poor prognosis.⁶

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Cetuximab

Cetuximab (Erbix, C225) is a human-murine chimeric immunoglobulin G (IgG) monoclonal antibody that competitively binds to the extracellular domain of EGFR and prevents binding by the natural EGFR ligands, the main of which are EGF and transforming growth factor- α (TGF- α). Among the entire panel of murine anti-EGFR antibodies, monoclonal antibody C225 was chosen for further clinical development for several reasons: it binds to the receptor with better affinity than the natural ligand; moreover, it also induces dimerization and downregulation of the EGF receptor which prevents further receptor binding and activation by the ligand. Potential clinical efficacy of cetuximab appears to involve multiple mechanisms, including inhibition of cell cycle progression, induction of apoptosis, inhibition of angiogenesis, inhibition of metastasis, and enhancement of the response to chemotherapy and radiation therapy.⁷

A phase I study of cetuximab was run by Baselga and colleagues who evaluated the pharmacokinetics and toxicity of cetuximab in 56 patients with advanced epithelial tumors over-expressing EGFR.⁷ Cetuximab was administered alone as a single dose in 14 patients, alone as weekly multiple doses in 17 patients and as weekly multiple doses in combination with cisplatin in 22 patients. Doses in the range of 200 to 400 mg/m² were associated with complete saturation of systemic clearance. Cetuximab infusion was well tolerated at the dose level tested and the most commonly reported toxicities were fever, asthenia, transaminase elevation, and skin toxicity.

Another similar phase Ib study⁸ has evaluated safety, pharmacokinetics and activity of cetuximab in combination with cisplatin in patients with advanced SCCHN. Twelve patients who had high levels of EGFR expression and tumors easily accessible for repeated biopsies (pretherapy, 24 hours after first C225 infusion, 24 hours before third C225 infusion) were entered at three different dose levels of C225 with a fixed dose of cisplatin. Both of the above studies indicated a loading dose of 400 mg/m² with a weekly maintenance dose of 250 mg/m² as the dose schedule to be recommended for further studies. Skin toxicity was the most common adverse event occurring in 70%–80% of patients, but it was rarely treatment limiting.

The aim of this review is to present and discuss the current and future role of cetuximab in the different subsets of SCCHN.

Recurrent/metastatic squamous cell carcinoma of the head and neck

Chemotherapy is the treatment of choice for recurrent/metastatic disease in patients not suitable for further

surgery or irradiation. Cisplatin is the most used drug in this setting and the combination of cisplatin and 5-fluorouracil (5FU) has represented the mainstay of first line treatment for the last twenty years. Several drugs have been used in combination with cisplatin and/or 5FU with the attempt to improve results.⁹

The taxanes have been shown to be active in SCCHN mainly in combination with cisplatin, but this activity has to be balanced against the mostly overlapping toxicity profile (in particular myelotoxicity and neurotoxicity). The combination of cisplatin and cetuximab has been studied in first line treatment of recurrent/metastatic disease. In particular, in the phase Ib study run by Shin and colleagues,⁸ treatment was feasible and hints of antitumor activity was observed. Burtneiss and colleagues¹⁰ carried out a phase III trial where 117 patients with recurrent/metastatic SCCHN were randomly assigned to receive cisplatin 100 mg/m² every four weeks with weekly cetuximab or placebo. Progression-free survival (PFS) was not statistically different between the two treatment groups. In particular, median PFS was 4.2 months for patients treated with cisplatin plus cetuximab and 2.7 months for patients treated with cisplatin plus placebo ($p = 0.09$). Median overall survival (OS) was also not statistically different between the two groups; (9.2 and 8.0 months, $p = 0.21$). Response rate was 26% and 10% in the two arms, respectively ($p = 0.03$). Patients treated with cisplatin and cetuximab experienced more frequently grade 3/4 toxicity which was mostly due to cisplatin. As expected, skin toxicity was more frequent in the experimental arm (37.7%) than in the control arm (23%) ($p < 0.001$). The issue of combining cetuximab with platinum (cis or carbo) and 5FU in recurrent metastatic disease was first addressed by Bourhis and colleagues in 53 patients. A substantially higher incidence of serious adverse events were observed in the cisplatin group (67%) than in the carboplatin group (32%); overall response rate was 36% and disease control rate was 74%, with no substantial difference between cisplatin and carboplatin. In the entire population time to tumor progression (TTP) was 155 days and median survival was 297 days.¹¹ This study paved the way to phase III evaluation. The EXTREME study, a phase III study comparing cisplatin-5FU with or without cetuximab, has provided evidence of statistically significant advantage in terms of locoregional control and overall survival for the experimental arm. In particular, median PFS was 5.6 months in the experimental arm and 3.3 months in the control arm ($p < 0.001$). Overall survival was 10.1 months vs 7.4 months in the experimental and in the control arm, respectively ($p = 0.04$). Overall response

rate was 36% vs 20% in the experimental and control arm, respectively ($p < 0.01$). As for toxicity, no differences in the grade 3/4 adverse events were recorded in the two arms.¹²

The prognosis for patients progressing after cisplatin containing regimen is very poor, with less than 5% response rate. On this basis, cetuximab has been tested in this setting.

Herbst and colleagues¹³ conducted a phase II trial in 131 patients who had obtained a stable disease (SD) or a progressive disease (PD) after a platinum-based chemotherapy. The combination of cetuximab and cisplatin was given to these patients who were divided into three subgroups: patients that had obtained a SD (SD cohort), patients that had obtained a PD after two cycles of CT (PD1 cohort) and patients that had obtained a PD after three or more cycles of CT (PD2 cohort). The objective response rate was 18% for the SD cohort, 20% for the PD1 cohort and 6% for the PD2 cohort. The median duration of response was 7.4 months for the SD cohort, 4.2 for the PD1 cohort and 4.1 for the PD2 cohort. Median overall survival for SD cohort was 11.7 months. The most common grade 3 and 4 cisplatin toxicities were myelosuppression and nephrotoxicity but there was no indication that cisplatin-based toxicity was exacerbated in combination with cetuximab, which induced the appearance of skin rash in 70% of patients.

Baselga and colleagues¹⁴ conducted a multicenter phase II trial of the combination of cetuximab and platinum therapy in patients with platinum-refractory SCCHN. Partial response (PR) and disease control rate was 10% and 53%, respectively. Median time to progression and overall survival were 72 and 150 days, respectively.

In patients who achieved a PR, the median TTP was 185 days and OS was 272 days. In addition, the median TTP and median OS were longer in patients receiving the three-week cycle compared with patients receiving the four-week-cycle. Skin reactions and acne-like rash occurred in 80% of patients, but only 3% of patients experienced a grade 3–4 cutaneous rash. This study demonstrated that the combination of cisplatin and cetuximab has a good activity in this population of platinum-refractory SCCHN patients and the results were particularly encouraging in view of the fact that more than half of the patients had received more than two cycles of platinum-based chemotherapy as first-line therapy.

The results of these two trials suggested that cetuximab given in association with cisplatin might have a role in reversing platinum resistance.

Moreover, cetuximab is effective also when given alone in patients with platinum-refractory SCCHN. In fact, Vermorken and colleagues¹⁵ tested single-agent cetuximab in a group

of 103 patients with SCCHN that had progressed after a platinum regimen. No patients achieved complete response, 13% of patients achieved a partial response while the disease control rate was 46%. The median TTP was 70 days and OS was 178 days. Progressive patients were switched to the cetuximab/cisplatin combination. In these patients, no objective responses were recorded but 27% of patients had a stable disease.

Cetuximab has been associated also to taxanes in patients with recurrent/metastatic disease. The combination of weekly docetaxel and standard cetuximab induced a 20% partial response rate and a 47% disease control rate in 45 patients.¹⁶ Paclitaxel was also evaluated in combination with platinum and cetuximab and a significant tumor response rate (56%) was observed.¹⁷

Locally advanced inoperable squamous cell carcinoma

Radiation therapy has been the treatment of choice in this subset of patients for several decades.⁹ However, clinical evidences now exist in favor of combined treatment approach, which includes chemotherapy and radiation therapy. In fact, several randomized trials have shown that adding concurrent chemotherapy to radiation significantly increases locoregional control. Furthermore, a recent meta-analysis reported an 8% increase in five-year survival with the combined approach.¹⁸ The common standard for chemotherapy in combination with radiation is cisplatin given at the dose of 100 mg/m². However, the combined administration of chemo and radiation therapy is significantly more toxic than radiotherapy alone, both in terms of acute toxicities (mucositis, dermatitis, leucopenia, emesis) and delayed toxicities (feeding tube dependence, pharyngeal and laryngeal dysfunction). Furthermore, the combined administration of chemo- and radiotherapy compromises postoperative adherence to further treatments¹⁹ and is associated with more frequent and longer treatment interruptions than radiation therapy; in turn, delays in radiation therapy delivery can adversely affect patient outcomes.¹⁹

It is well known that tumor cell repopulation during treatment is implicated as a cause of treatment failure after primary radiotherapy.²⁰ However, several studies have reported that repopulation of epithelial tumor cells after exposure to radiation is related to the activation and expression of EGFR.^{21–22} These findings suggest that EGFR blockade may be important in reducing tumor cell repopulation after radiotherapy and this strategy may improve tumor control.

Several preclinical studies have investigated the effect of combined C225/radiation treatment in cell lines derived from human SCCHN.²³ Such combined treatment resulted in a strong decrement in cellular proliferation. Saleh and colleagues demonstrated that, in cell lines derived by human SCCHN, addition of C225 to radiation treatment was able to inhibit cellular proliferation by approximately 35% for the lowest EGFR expressing cell lines and by 70% for the highest expressing cell lines.²⁴

A phase I trial of cetuximab and radiation therapy was carried out at the University of Alabama.²⁵ Thirteen of 15 patients achieved a complete response whereas a partial response was seen in the remaining two patients. Median duration of response was 28 months and toxicity data highlighted the safety of this approach without the need of dose modification. Recently Bonner and colleagues published a phase III trial comparing radiotherapy alone with the combination of cetuximab and radiotherapy in locally advanced inoperable SCCHN (424 patients). The experimental arm showed a statistically significant superiority in locoregional control and overall survival; in particular, duration of locoregional control was 24.4 months with combined treatment and 14.9 months ($p = 0.005$) in the control arm. Median survival time was 49 months in the experimental arm and 29.3 months in the control arm ($p = 0.03$); median PFS was 17.1 months and 12.4 months in the two arms respectively ($p = 0.006$). Cetuximab did not worsen the main toxicities associated to radiotherapy.²⁶ Quality of life (QoL) in these patients was assessed by Curran and colleagues²⁷ in a follow-up analysis in which QoL was assessed using two different questionnaires, the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 which evaluates functioning and symptoms common to most cancer patients, and the QLQ HeN35 which evaluates symptoms specifically associated with head and neck cancer and its treatment. Compliance with completion of QoL questionnaires was high in both arms and, most importantly, there was no significant difference in QoL scores between the two treatment arms.

Cetuximab is now approved for use in combination with exclusive radiation treatment in patients with diagnosis of locally advanced inoperable SCCHN.

The following logical step was to combine cetuximab with radiation therapy and chemotherapy. Pfister and colleagues²⁸ conducted a phase II study of a combined regimen of weekly cetuximab administered with conventional schedule and associated to standard cisplatin and radiotherapy. A total of 22 patients were enrolled in the study. Mucositis, skin rash, nausea, and vomiting were the main observed toxicities.

This study was closed early because of five serious adverse events including two deaths, one myocardial infarction, one bacteremia, and one atrial fibrillation. Three complete responses and 13 partial responses were observed in the 16 assessable patients. Three-year PFS and overall survival rate were 56% and 76%, respectively. However, this regimen was not recommended for further evaluation due to heavy toxicity. Similar results were reported by Merlano and colleagues.²⁹ The response rate was 100%, but impressively high toxicity was reported with particular regard to skin toxicity. Kuhnt and colleagues³⁰ evaluated the combination of concomitant hyperfractionated accelerated radiotherapy (HART) with cisplatin and cetuximab. Fourteen patients were treated and a response rate of 91% was achieved. The treatment was well tolerated and weekly cisplatin at the dose of 40 mg/m² was recommended in combination with cetuximab plus HART.

The role of induction chemotherapy in patients with locally advanced inoperable disease has gained considerable interest in the last two years with the publication of two phase III trials of docetaxel, cisplatin, 5FU vs cisplatin, 5FU. The first study was carried out by the EORTC.³¹ Patients were randomized to receive four cycles of either TPF (docetaxel and cisplatin 75 mg/m² on day one, 5FU 750 mg/m²/day, for five days of continuous infusion) or standard PF (cisplatin 100 mg/m² on day one, 5FU 1000 mg/m² daily for five days of infusion). Radiation therapy was subsequently administered. PFS was higher in the experimental arm (11.0 vs 8.2 months, $p = 0.007$). Median overall survival was 18.8 months vs 14.5 months (hazard ratio = 0.73). Response rate was also significantly higher in the experimental arm (68% vs 54%, $p = 0.006$). Complete response rate was 9% vs 6%, $p = \text{n.s.}$ Although neutropenia, as expected, was more frequent in the TPF arm, the toxic death rate was 2.3% in the TPF arm and 5.3% in the PF arm. Quality of life was also better in patients in the TPF arm ($p = 0.01$). The second phase III study was carried out by Posner and colleagues.³² The treatment plan was very similar to the other study and three cycles of TPF (docetaxel 75 mg/m², cisplatin 100 mg/m² on day one, 5FU 1000 mg/m² daily for four days of continuous infusion) were compared with three cycles of standard PF. Radiation therapy was administered for seven weeks and was combined with weekly carboplatin therapy. Overall survival was higher in the TPF group (71 vs 30 months, respectively; $p = 0.006$); locoregional control was also better in the TPF group ($p = 0.04$). Overall response rate favored the experimental arm (72% vs 64%), but the difference was

not significant. These two studies have represented a major breakthrough and have provided evidence that induction chemotherapy followed by irradiation can represent the best option in many cases. The next step is how to optimally integrate induction chemotherapy with cetuximab therapy in order to further improve treatment outcome by giving patients all the most effective therapeutic options in first line of treatment.

Kies and colleagues³³ reported a study of induction chemotherapy with weekly paclitaxel, carboplatin and cetuximab in patients with inoperable disease. Complete response rate, which was the main endpoint of the study, was observed in 83% of 47 evaluable patients at the primary site and in 27% at the nodal site. Hematologic and skin toxicities were the only observed grade 3/4 adverse events. The Eastern Cooperative Oncology Group (ECOG) has evaluated the combination of cetuximab, paclitaxel and carboplatin followed by cetuximab, carboplatin and radiation therapy in patients with locally advanced SCCHN. A high rate of complete pathological responses at the tumor site was observed; in particular 40/63 patients were clinical responders at week 8 after induction therapy. Among these, 63% of patients had complete pathological response at week 14 after chemoradiotherapy. Grade 4 neutropenia was the main adverse event being observed in 14% of patients.³⁴ Tishler and colleagues have recently presented a phase I study of cetuximab added to TPF induction chemotherapy. This was conceived as phase I study because of 5FU escalation in association with standard doses of docetaxel, platinum and cetuximab. Preliminary results showed 11 partial responses out of 15 evaluable patients. 850 mg/m² was the 5FU selected dose.³⁵ A retrospective analysis of addition of cetuximab to induction TPF has been performed by Kuperman and colleagues. Standard doses of the four drugs were used; overall response rate was 71% in 21 enrolled patients; the toxicity profile was foreseeable and mild.³⁶ Argiris and colleagues have recently reported a phase II study of neoadjuvant docetaxel, cisplatin and cetuximab followed by concurrent radiation, cisplatin and cetuximab in locally advanced SCCHN. The overall response rate to induction chemotherapy was 86% in 37 evaluable patients. After the combined chemoradiotherapy the overall response rate was 100%. Hematologic and skin toxicities were the most relevant adverse events also in this study.³⁷ Langer and colleagues have presented preliminary data of the ECOG 3303 study in which concurrent radiotherapy, cisplatin and cetuximab was given to 61 patients. The overall response rate was only 48% in this study. Moreover, a number of

relevant adverse events including a death from neutropenic fever were observed.³⁸ Bonnin and colleagues administered induction TPF (docetaxel 75 mg/m² on day 1, cisplatin 75 mg/m² on day 1 and fluorouracil 750 mg/m² on day 1–5, to be repeated every 21 days for 3 cycles) followed by concurrent chemoradiotherapy (cisplatin or cetuximab) in 123 patients with unresectable SCCHN. The overall response rate was 96% after induction chemotherapy, but subsequent chemoradiotherapy turned out to be very toxic showing a 64% of grade 3–4 toxicity.³⁹

Taken as a whole, these data show that appropriate integration of cetuximab, radiotherapy and induction chemotherapy have the possibility to improve treatment outcome in the near future. The results of completed and ongoing studies of cetuximab in the different subsets of patients with SCCHN are summarized in Tables 1 and 2.

New perspectives

The importance of cetuximab in the therapeutical armamentarium against SCCHN has considerably increased. The concomitant use of chemoradiotherapy and cetuximab has not matched the expectation, but its role is being revisited.

The Radiation Therapy Oncology Group (RTOG) is running a phase III randomized trial of chemoradiotherapy vs chemoradiotherapy plus cetuximab in patients with stage III/IVa squamous cell carcinoma of the oropharynx, hypopharynx or larynx. After stratification by site of primary, performance status, regional nodes, patients are to receive cisplatin conventional dose plus accelerated radiotherapy and concomitant boost with or without the addition of cetuximab at the common dose schedule.

Evaluation of cetuximab in the adjuvant setting is a further way to explore the potential of this compound. RTOG is running a randomized trial in locally advanced resected patients judged at high risk of relapse. Patients are randomized to receive radiation therapy plus cetuximab plus weekly cisplatin in the arm A and radiotherapy plus cetuximab plus weekly docetaxel in the arm B. On the other hand, another phase III trial is being conducted in patients with intermediate risk of relapse. Patients are randomized to receive either radiation therapy alone or cetuximab plus radiation therapy. Preliminary results are not yet available for each of the two studies; however, they are eagerly awaited since they are going to provide information on the possible usefulness of cetuximab also in the adjuvant setting.

An appealing new strategy involves the combination of different EGFR-targeted therapies, ie, the combined administration of a monoclonal antibody and a tyrosine

Table I Completed clinical trials with cetuximab in SCCHN

Trial	N. patients	Phase	Design	Endpoints	Results	Setting
Burtneß et al ¹⁰	117	III	CDDP-cetuximab ^a vs CDDP	OS PFS ORR	Not significant Not significant Significant (p = 0.03)	First-line Recurrent/metastatic
Bourhis et al ¹¹	53	II	CDDP-5FU-cetuximab	ORR	36%	First-line Recurrent/metastatic
Vermorken et al ¹²	442	III	CDDP-5FU-cetuximab ^a vs CDDP-5FU	OS PFS ORR	Significant (p = 0.04) Significant (p = 0.001) Significant (p = 0.001)	First-line Recurrent/metastatic
Herbst et al ¹³	132	II	CDDP-cetuximab	ORR	12,8%	Second-line (Platinum-refractory) Recurrent/metastatic
Baselga et al ¹⁴	96	II	CDDP-cetuximab	ORR	10%	Second-line (Platinum-refractory) Recurrent/metastatic
Vermorken et al ¹⁵	96	II	Cetuximab	ORR	13%	Second-line (Platinum-refractory) Recurrent/metastatic
Bonner et al ²⁶	424	III	Radiotherapy-cetuximab ^a vs Radiotherapy	PFS OS ORR	Significant (p = 0.005) Significant (p = 0.003) Significant (p = 0.02)	Locally advanced disease
Pfister et al ²⁸	21	II	Radiotherapy-CDDP + cetuximab ^a vs Radiotherapy-CDDP	ORR	94%	Locally advanced disease

Notes: ^aExperimental arm.

Abbreviations: OS, overall survival; PFS, progression free survival; ORR, overall response rate.

kinase inhibitor. A sound preclinical rationale for this approach does exist. In fact, while monoclonal antibodies require an intact EGFR ligand binding domain, tyrosine kinase inhibitors are also active against mutated forms of the EGFR. Furthermore, monoclonal antibodies can also elicit antibody-dependent cellular cytotoxicity. Matar and colleagues⁴⁰ have evaluated the combination of gefitinib and cetuximab in a panel of human cancer cell lines and in an EGFR-dependent human tumor xenograft model (A431). The combined treatment with the two agents resulted in a synergistic effect on cell proliferation, a greater inhibition of EGFR-depending signal and induction of apoptosis. In *in vivo* experiments single agent gefitinib or cetuximab induced transient complete remission only at the highest doses, while suboptimal doses of both drugs given in combination induced complete and permanent regression of large tumors with a greater inhibition of EGFR, MAP-K, and AKT phosphorylation. The evaluation of cDNA arrays showed that while 59 genes were coregulated by the two agents, 45 genes were differentially regulated, strengthening the rationale of the combined administration. Huang and colleagues⁴¹ evaluated the potency of EGFR inhibition in a variety of human cancer cell lines after treatment with

combination of cetuximab and either gefitinib or erlotinib. The combination enhanced growth inhibition over that observed with either single agent alone. *In vivo* data confirmed that higher tumor regression and growth delays were observed in mice treated with the combination. Taken as a whole, these studies may pave the way to clinical evaluation of combinations of EGFR-targeted agents.

Simultaneous targeting of multiple pathways is an attractive strategy of cancer treatment. In particular, the combined use of drugs targeting EGFR and vascular endothelial growth factor (VEGF) pathways is an appealing approach since angiogenesis has been associated with tumor progression and worse outcomes. Furthermore VEGF is often upregulated in tumors resistant to anti-EGFR compounds. Most of the clinical studies which have been run with the combination of anti-EGFR and anti-VEGF compounds have involved erlotinib and bevacizumab. However, early results of a clinical trial involving the combination of cetuximab and bevacizumab have been presented in patients with recurrent/metastatic SCCHN that had progressed after a prior line of chemotherapy.⁴² This combination showed a good clinical activity with a disease control rate of 80%. Further trials are needed to confirm this encouraging result.

Table 2 Ongoing clinical trials with cetuximab in SCCHN

Trial	N. patients	Phase	Design	Endpoints	Results	Setting
Kies et al ³³	47	II	CBDCA-paclitaxel-cetuximab (induction)	CRR	27%	Locally advanced disease
Tishler et al ³⁵	15	I	CDDP-docetaxel-5FU + cetuximab 5FU escalating dose 750→1000 mg/m ² (induction)	ORR	73%	Locally advanced disease
Kuperman et al ³⁶	21	II	CDDP-docetaxel-5FU + cetuximab (induction)	ORR	71%	Locally advanced disease
Argiris et al ³⁷	37	II	CDDP-docetaxel + cetuximab (induction) followed by CDDP + radiotherapy	ORR	100%	Locally advanced disease
Langer et al ³⁸	61	II	Radiotherapy-CDDP + cetuximab	ORR	48%	Locally advanced disease
Bonnin et al ³⁹	123	II	CDDP-docetaxel-5FU followed by radiotherapy-CDDP + cetuximab	ORR	96%	Locally advanced disease

Abbreviations: CRR, complete response rate; DCR, disease control rate; ORR, overall response rate.

Finally, the relationship between the RAS gene family, particularly K-ras, and tumorigenesis has generated considerable interest. In particular, the occurrence of K-ras mutation has been associated with the effectiveness of cetuximab and other drugs interfering with EGFR signaling in advanced colorectal cancer.⁴³ As for head and neck cancer, overexpression and mutation of members of the RAS gene family have been observed more rarely,^{44–45} but clinical trials in this setting are well worth undertaking.

Disclosures

The authors report no conflicts of interest in this work.

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