Review of cetuximab in the treatment of squamous cell carcinoma of the head and neck

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Abstract: Cetuximab is a monoclonal antibody able to inhibit and to degrade the transmembrane receptor Her-1, also known as epidermal growth factor receptor (EGFR). The inhibition of EGFR is of major importance since the receptor influences many important tumor cell activities including tumor growth, neo-angiogenesis, inhibition of the apoptotic response to chemotherapy and radiotherapy. Available experimental data suggest that cetuximab may enhance chemotherapy and radiotherapy activity, reverse resistance to some anticancer drugs and has itself anticancer activity. Early clinical data support experimental results. This paper reviews the published experiences on cetuximab in the treatment of advanced head and neck cancer and points out the future objectives of the clinical research on this drug.

Keywords: cetuximab, head and neck neoplasms

Background

Cetuximab recently received both the FDA and EMEA approval for the treatment of patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN). Cetuximab is a chimeric human- murin immunoglobulin G1 (IgG1) monoclonal antibody that binds the epidermal growth factor receptor (EGFR) with high specificity and competitively inhibits endogenous ligand binding (Sato et al 1983; Gill et al 1984; Goldstein et al 1995). The link between cetuximab and EGFR induces receptor dimerization, internalization and degradation (Fan et al 1994; Schlessinger 2000; Herbst and Shin 2002).

EGFR is a 170-kd transmembrane glycoprotein, member of the ErbB family of tyrosine kinase receptors, composed by an extra cellular ligand-binding domain, a trasmembrane lipophilic segment and an intracellular protein kinase domain with a regulatory carboxyl terminal segment. After binding with its ligands, EGFR occurs dimerization, posphorylation of the tyrosin kinase, activating the receptor pathway, internalization and degradation (Thomson and Gill 1985; Schlessinger 1988; Carpenter and Cohen 1990; Ulrich and Schlessinger 1990; Olayioye et al 2000; Schleissinger 2000; Yarden and Sliwkowski 2001; Mendelsohn and Baselga 2003; Hynes and Lane 2005).

In SCCHN the EGFR overexpression is associated with more aggressive disease, increased resistance to chemotherapy and radiotherapy, increased metastasis, inhibition of apoptosis, promotion of neoplastic angiogenesis, and, finally, poor prognosis and decreased survival (Santini et al 1991; Grandis et al 1998; Nicholson et al 2001; Ang et al 2002, 2004; Gupta et al 2002; O-Charoenrat et al 2002; Eriksen et al 2004). However, experimental studies demonstrated that the blockade of EGFR by monoclonal antibodies (Mabs) or by tyrosin- kinase inhibitors reverts radio resistance and enhances radiosensivity and chemosensivity in human SCCHN cell lines in vitro and in vivo (Goldstein et al 1995) .

In clinical practice, EGFR expression is evaluated using a standardized immunoistochemistry (IHC) assay, designated to asses cell membrane staining. EGFR

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expression is reported by the maximal intensity of the IHC stain in the cytoplasm on an ordinal scale of 0 to 3 (Goldstein et al 1995; O-Charoenrat et al 2002). Unfortunately IHC is a semi-quantitative methodology allowing wide inter-lab-differences. Moreover it has not yet been shown any quantitative relationship between EGFR expression and clinical response to its inhibition, so that the role of EGFR expression to predict response to EGFR targeting agents is unclear.

Cetuximab and radiotherapy

Robert et al (2001) evaluated a combination of escalating doses of cetuximab concurrent with radiotherapy in a phase I study. The momoclonal antibody was given from 100 to 500 mg/m2 loading dose and from 100 to 250 mg/m2 weekly maintenance dose to patients with SCCHN. Cetuximab did not worse the usual radiation therapy side effects and added only mild to moderate skin reaction. Unfortunately one patient was removed from the study, due to grade IV anaphylactic reaction. Objective responses were achieved in all the patients and they were complete in most cases. In conclusion Robert at al showed that cetuximab can be added to RT at the standard clinical dose (400 mg/m2 loading dose and 250/m2 weekly maintenance doses) without any dose limiting toxicity.

On these bases Bonner et al (2006) conducted and published a phase III trial. In this study 424 patients with locoregional advanced head and neck cancer were randomly assigned to radiotherapy alone or the same radiotherapy plus weekly cetuximab at the standard clinical dose. The accrued patients had stage III or IV not previously treated, histologically proven, squamous cell carcinoma arising from oropharinx, hypopharinx and larynx. Overall 13 pts discontinued cetuximab, mostly because of hypersensitivity reactions (4 pts) or acneiform rush (8 pts). With the exception of these toxicities, the incidence of severe reactions was similar in the two treatment arms confirming that cetuximab does not exacerbate the common radiotherapy related side effects (Table 1). The experimental arm significantly improved loco-regional control and median survival: 24.4 months vs 14.9 ($p = 0.005$) and 49 vs 29.3 months ($p = 0.03$) respectively, compared to radiotherapy alone. Thus the Bonner's trial shows that cetuximab plus radiotherapy is superior to radiotherapy alone. Interestingly, this is the first trial showing that the results of radiotherapy can be significantly improved by the addition of a drug without worsening radiotherapy toxicity.

The weakness of the Bonner's trial is its control arm, since radiotherapy alone is no longer the standard treatment of most SCCHN patients. Indeed a number of meta-analyses have shown that chemo-radiation is a more appropriate standard treatment in advanced unresectable SCCHN (Merlano and Marchetti 2003).

However radiotherapy remains a good option when adequate clinical expertise is not available or in any other

Table 1 Comparison of major toxicities according to treatment plan (% of patients)

	Column A RT cetuximab[a]	Column B RT cisplatin cetuximab[b]	Column C cisplatin cetuximab[c]	Column D RT alone[a]	Column E cisplatin + placebo[c]	Statistical significance
Mucositis	56	24	0	52	0	ns
Acneiform rash	17	23	16	1	0	Column A vs D $p < 0.001$ Column C vs E $p < 0.001$
Dehydration	6	33	12	8	10	ns
Anemia	1	9.5	15	6	9	Column A vs D $p = 0.006$
Allergic reaction	3	4.8	6	0	2	Column A vs D $p = 0.01$
Infection	1	9.5	15	1	10	ns
Hypomagnesemia	NS	NS	13	NS	0	Column C vs E $p = 0.006$

Most common grade 3–5 adverse events that occurred or reached a difference statistically significant.
RT, radiotherapy; NS, not stated; ns, not significant.
[a]From Bonner et al (2006).
[b]From Pfister et al (2006).
[c]From Burtness et al (2005).

situation precluding chemotherapy. The Bonner trial suggests that in these conditions radiotherapy and cetuximab should be regarded as the new standard. On the contrary it is unclear whether cetuximab may be as effective as chemotherapy combined with radiotherapy, due to the lack of comparative trials.

Cetuximab and chemotherapy

It has been suggested that palliative chemotherapy may achieve advantage in quality of life and a survival over best supportive care (Stell et al 1983; Constenla et al 1997; Leon et al 2004). However all the patients with recurrent disease not suitable for savage surgery and/or radiotherapy, will die of their disease, eventually.

Due to the poor outcome of these patients there is a need for new active agents. Cetuximab may theoretically play an important role in this setting of patients: the different mechanism of action compared to conventional chemotherapeutic drugs should favor the lack of cross resistance and the poorness of side effects should allow the treatment of patients with low performance status.

Trigo et al (2004) evaluated cetuximab alone in 103 patients refractory to cisplatin based chemotherapy. The most frequent adverse event was skin rash/acne reaction which happened in 80% of patients (1% grade 3). There was one treatment related death due to hypersensitivity reaction.

Seventeen patients achieved an objective response including 5 complete responses (Objective Response Rate 16.5%) and the median survival of the whole patients population was 5.9 months. Both the response rate and the median survival are similar to that expected with platinum alone in chemotherapy naive patients (Forastiere et al 1992). The observed activity and the limited toxicity prompt the Researchers to test cetuximab in combination with chemotherapy.

Baselga et al (2000) was the first to report phase I clinical trials testing the feasibility of combining cisplatin and cetuximab. The study end points were to establish safety profile, to determine the optimum biologic dose, the maximum tolerated dose and the pharmacologic profile of cetuximab alone or in combination with cisplatin. Fifty-two patients were treated in three successive phase I clinical trials in which cetuximab was given as a single dose (13 pts), weekly multiple dose (17 pts) and weekly multiple dose with cisplatin (22 pts). These trials demonstrated the safety of cetuximab given alone or in combination with chemotherapy.

Bourhis in a further trial evaluated the combination of cetuximab with cisplatin, or carboplatin, and fluorouracil. The treatment was tolerable allowing full dose of the cytotoxic agents, due to the absence of overlapping toxicities (Bourhis et al 2006).

Therefore, cetuximab can be safely added to chemotherapy, and, considering the different toxic profile and its demonstrated activity, could improve chemotherapy results. On these bases Burtness et al (2005) conducted a double-blind randomized phase III trial comparing cisplatin and cetuximab (arm A) with cisplatin and Placebo (arm B). The combination arm experienced significantly more frequent neutropenia, hypomagnesemia and skin toxicity. Skin toxicity in particular was 77% in arm A (grade 3 in 23%) and 24% in arm B (no grade 3). Surprisingly hypersensitivity were expressed in both arms, 3% of grade 3 and 3% of grade 4 in arm A, 2% of grade 3 and 0% grade 4 in arm B (Table 1). The combination of cetuximab and cisplatin gave a significant higher response rate than placebo and cisplatin (36% vs 10%, p 0.03). The response rate for the patients in arm A who developed skin toxicity was 33% compared to 7% in patients who did not. This difference is not statistically significant ($p = 0.08$). However skin toxicity was associated with a statistically significant survival improvement ($p = 0.01$). The progression free survival (PFS) and the overall survival (OS) showed a trend in favor of arm A, but did not meet the statistical significance. This study demonstrated that cetuximab increases the antitumor activity of cytotoxic chemotherapy and that survival is improved in patients developing skin reaction. Even Salz et al (2003), described the relationship between skin rush and prolonged survival in an earlier report.

An additional way to employ cetuximab and chemotherapy arises from the relationship between EGFR overexpression and drug resistance. EGFR phosphorilation results in the activation of multiple pathways including PI3K- AKT. This way enhances BCL-2 activity, inhibiting the apoptotic response to chemotherapy and radiotherapy. Thus the inhibition of EGFR should downregulate BCL-2 activity, restoring apoptotic response to chemotherapy and radiotherapy (Huang et al 1999; Huang and Harari 2000; Harari and Huang 2001). This is why cetuximab has been combined with some chemotherapeutic drugs, to treat patients with already demonstrated refractory disease to the same drugs.

Herbst and Baselga respectively conducted and published two phase II trials in platinum refractory patients with SCCHN. Herbst et al (2005) treated with cetuximab and cisplatin patients not responders to, or progressed during, cisplatin/paclitaxel or cisplatin/fluorouracil. Patients accrued were grouped in 3 groups according to response to prior regimen: group 1 = stable disease, group 2 = on treatment progressive disease, group 3 = progression within 90 days

from the end of therapy. Patients received cetuximab at the conventional clinical dose and cisplatin 75 or 100 mg/m^2 every 3 weeks. Cetuximab did not show any effects on pharmacokinetic profile of cisplatin and cisplatin-based toxicity was not exacerbated by cetuximab. The objective response rates were 18%, 20%, and 6% in the three groups respectively. The PFS and the OS were greater in group 1 (4.2 and 11.7 months) compared to group 2 (3 and 6.1 months) and group 3 (2 and 4.3 months).

Baselga et al (2005) treated 96 patients platimum refractory, with cetuximab and cisplatin or carboplatin according to an every 3 weeks scheduling or an every 4 weeks. The response rate was 10% with 53% of disease control rate. The median time to progression (TTP) and the overall survival (OS) were 85 and 183 days. There was a trend in favor of partial responders in terms of TTP and OS, and, similarly in patients treated with the every 3 weeks schedule compared to every 4 weeks. The skin reaction and acne – like rash were the most common adverse events, 80% and 72% respectively. They were grade 3 in 2% and grade 4 in 1%. The patients who developed a grade 1 or 2 skin reaction achieved a prolonged TTP and OS.

These studies can be interpreted in two ways: The first is that cetuximab can reverse cisplatin resistance in a small but significant number of patients without any major additional toxicity; the second is that cetuximab could be the only drug achieving interesting response rate in second line treatment of advanced SCCHN. Data on activity of cetuximab in advanced head and neck cancer are summarized in Table 2.

Cetuximab and chemoradiation

As stated above, chemo-radiation is the standard of care for most patients with SCCHN. Data on cetuximab combined with chemo-radiation are lacking. At present there are two main unanswered questions on this matter. The first is whether cetuximab combined with radiotherapy may be at least as effective as chemo-radiation. We have no way to answer this question, unless a comparative randomized trial is performed. In our knowledge, there are no such published trials.

The second question is whether cetuximab may add to chemo-radiation in terms of major end-points: survival, disease free survival and complete responses. This second question is more complex and requires multi-level evaluation. The first level is to understand whether cetuximab can be safely added to chemo-radiation. The second is to point out the appropriate dosage and scheduling. The third is to investigate whether the level of activity of such combination may be of interest for future phase III trials. The last step is to compare chemo-radiation to the same plus cetuximab in a randomized setting.

To day only Pfister et al (2006) reported a trial of chemo-radiation combined with cetuximab in a full paper. All the evaluable patients entering this study achieved an objective response, but two grade V events occurred, leading the Authors to close the trial in advance. The investigators considered the relationship between the two on treatment deaths and the investigational regimen, uncertain. However, additional non fatal, but significant adverse events occurred prompting study closure. The major toxicities encountered by Pfister et al are listed in Table 1.

However, at 3 years median follow-up, PFS and OS were 59 e 76% respectively suggesting a favorable effect by the addition of cetuximab to chemoradiation. The authors concluded that the search for a less toxic regimen combined cetuxumab and chemo-radiation is highly recommended (Pfister et al 2005).

The Authors' group reported in abstract form an on-going experience of rapidly alternating chemoradiation and cetuximab (Merlano et al 2005). Alternating chemo-radiation is a minor variation of concurrent chemo-radiation aimed to reduce toxicity (Merlano 2006). This is why we are using this approach in a phase II trial of combined chemo-radiotherapy and cetuximab. At present, 31 patients have been accrued and 18 are fully evaluble. No major toxicity occurred and

Table 2 First line palliative treatment of advanced SCCHN

	Responders	Non responders	NE	PFS	OS
Cetuximab[a]	16.5%	82.5%	1%	2.8 m	5.8 m
Cisplatin and Placebo[b]	10%	90%		2.7 m	7.9 m
Cisplatin and Fluorouracil[c]	29.8%	59.6%	10.6	NS	8.7 m
Cisplatin and Paclitaxel[c]	26%	60%	14	NS	8.1 m
Ciplatin and Cetuximab[b]	26%	74%		4.2 m	9.2 m

NE, not evaluable; PFS, progression free survival; OS, overall survival; m, months; NS, not stated.
[a]Trigo et al (2004).
[b]Burtness et al (2005).
[c]Gibson et al (2005).

all the patients achieved an objective response, including 13 complete responses. The study has a planned accrual of 45 patients; therefore, the final analysis is foreseen within 2007. Other phase II studies of chemo-radiation and cetuximab are in progress worldwide and results of some of these are expected soon. Notwithstanding the lack of definitive data from phase II studies, the RTOG has designed and activated a phase III trial of definitive chemo-radiation plus or minus cetuximab (Harari and Huang 2006). Data will be available in the forthcoming years.

Therefore we cannot understand yet the true role of the combination of cetuximab and chemo-radiation in SCCHN, due to the lack of definitive data; this treatment must be still regarded as an experimental approach not to use outside of clinical trials.

Conclusion

Cetuximab is the first monoclonal antibody showing clinical activity in SCCHN. Available data support its use in patients refractory to platinum/fluorouracil or platinim/paclitaxel. Preliminary data also suggests that cetuximab can be given in combination with cisplatin in chemotherapy naïve patients, with positive impact on response rate and overall survival. It is possible that, if cetuximab will be added to a more standard palliative chemotherapy, ie, cisplatin and paclitaxel or cisplatin and fluorouracil, the benefit could be more evident. Moreover, further investigations should take into account the end point "quality of life" systematically including the use of validate questionnaires.

More convincing data suggest the use of cetuximab in combination with radiotherapy, at least in patients not candidate for chemo-radiation. The results of the Bonner's trial showed not only significant improvements in all the major and-points, but also that radiotherapy toxicity remained unchanged notwithstanding the addition of cetuximab. We have not yet randomized phase III trials comparing chemo-radiation and cetuximab-radiation, but considering that chemo-radiation is a highly toxic treatment, such trial is recommended.

Finally, the combination of cetuximab and chemo-radiotherapy is a field almost completely uninvestigated. The only published trial recorded two on treatment deaths, but their relationship with the addition of cetuximab is unclear. Other preliminary data from ongoing studies do not show any significant worsening of toxicity at the moment. However, available data are inadequate to suggest the use of cetuximab during a chemo-radiotherapy program outside clinical trials.

In conclusion, cetuximab represents an important new drug in the management of SCCHN. Furthermore clinical investigations on cetuximab are still ongoing. Therefore additional advantage by the introduction of cetuximab in the daily clinical practice may be expected in the future.

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