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REVIEW ARTICLE

The efficacy of combined treatment with cetuximab (erbitux) and radiation therapy in patients with head and neck cancer

G. Koukourakis[1], V. Kouloulias[1], M. Koukourakis[2], J. Kouvaris[1], G. Zacharias[3], A. Gouliamos[1]

[1]University of Athens, Medical School, 2nd Department of Radiology, Radiation Therapy Unit, "Attikon" University Hospital, Athens; [2]University Hospital of Thrace, Radiation Therapy Unit, Alexandroupolis; [3]Polyclinic of Athens, Section of Pathology, Athens, Greece

Summary

Squamous cell carcinoma of the head and neck (SCCHN) region is among the most frequent human tumors due to the alcohol and tobacco abuse. Its management has evolved gradually from surgery as the mainstay of therapy to irradiation as the principal treatment. When radiation therapy is combined with chemotherapy, additional benefit is obtained. The value of chemoradiotherapy (CRT) is, however, counterbalanced by increased and often prohibitive toxicity, particularly among patients with coexisting medical conditions and decreased performance status. A member of the ErbB family of receptor tyrosine kinases known as the epidermal growth factor receptor (EGFR) is abnormally activated in epithelial cancers, including head and neck cancers. Overexpression of EGFR is a feature associated with poor clinical outcome. It is observed that radiation increases the expression of EGFR in cancer cells and the blockade of EGFR signaling sensitizes cells to the effects of radiation. The cytotoxic effects of radiation therapy in squamous cell carcinoma could be enhanced by cetuximab (erbitux), a monoclonal antibody against the ligand-binding domain of EGFR. The major studies that focus on the efficacy of adding cetuximab to radiotherapy in the treatment of patients with head and neck cancer and its impact in quality of life are reviewed in this study.

Key words: cetuximab, chemoradiotherapy, head and neck cancer, radiotherapy

Introduction

Neoplasms of the head end neck region, mainly squamous cell carcinomas of the pharynx, larynx and oral cavity, account for over 5% of all malignancies. Worldwide, in 2002, there were in excess of 500.000 new cases and over 300.000 deaths attributed to this disease [1]. In locally advanced disease, surgery and/or radiation, sometimes combined with chemotherapy, are commonly used for treatment [2]. Nevertheless, after surgery, a considerable proportion of patients relapse locally or at distant sites [3]. Moreover, the long-term treatment outcome of patients with locally advanced disease seems to be poor with conventional schedules of radiotherapy; locoregional disease control is observed in approximately 30% of patients [4,5] with 5-year survival rates of only 15-25% [6] and median survival of approximately 12 months [7]. Due to lack of success of the treatments available for locally advanced SCCHN, the research for new approaches has resulted in the development of alternative radiotherapy fractionation schedules, such as hyperfractionation and accelerated fractionation with concomitant boost [8,9]. Both of the above schedules have shown better efficacy regarding the locoregional control compared to standard fractionation [10].

Apart from that, attempts have been made to incorporate the administration of systemic chemotherapy into radiotherapy schedules, while some of the cytotoxic agents are already being used as radiosensitizers [5,11,12]. This approach was based on increasing tumor cell killing at the site of primary disease, as

Correspondence to: Georgios Koukourakis, MD. Rimini 1 Street, Haidari, 124 64 Athens, Greece. Tel: +30 210 5831860, Fax: +30 210 5326418, E-mail: gkoyokoyrakis@yahoo.gr

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well as on targeting distant micrometastases that may be present at the time of the primary treatment [13]. This has led to the implementation of highly effective regimes, which has resulted in a significant increase of treatment efficacy in terms of locoregional control and survival [5, 11]. Nevertheless, the cost of that increase in efficacy was the increased toxicity, particularly in relation to severe acute side effects, detected in a significant number of patients. Subsequently, the treatment compliance was poor and observed in almost one third of the cases, mostly in those who had received cisplatin 100 mg/m^2 every 3 weeks [5,11].

Therefore, there was a need for new treatment combinations based on drug-radiotherapy interactions and for developing protocols integrating novel approaches, so that highly efficient agents be able to exert synergistic effects with radiotherapy as well as increasing its efficacy.

Biological targeted agents; the role of cetuximab in anticancer treatment

Lately, new anticancer drugs have been designed and tested to interact with defined tumor-associated molecular targets. That fact has raised hope that targeted drugs will be very effective and well tolerated too. In order to optimize the therapeutic index, the selective inhibition of tumor cell repopulation after radiotherapy, while, at the same time, leaving normal tissues unaffected, is one possible approach [17]. Agents that target EGFR, a member of an important family of transmembrane signaling proteins, are of great interest [18]. EGFR signaling is associated with control of normal cell growth and differentiation as well as tumorigenesis and disease progression in malignant tissues [19]. High expression of EGFR levels has been observed in a variety of solid tumors, including SCCHN in which almost all lesions showed EGFR expression on immunohistochemistry (IHC) analysis [20-22]. It is also known that EGFR mediates the resistance of cancer cells to radiation in a manner proportional to the degree of receptor expression [23]. The implication of high levels of expression in the therapeutic outcome [24,25] has focused on the importance of EGFR as an anticancer drug target [26,27].

Cetuximab is an IgG1 monoclonal antibody which specifically targets the EGFR with high affinity and inhibits competitively endogenous ligand binding. This action inhibits receptor signal transduction, directly by preventing the EGFR monomer from adopting the extended configuration necessary for dimerization, and indirectly by stimulating EGFR internalization and degradation [28]. The result of EGFR blockade is the inhibition of cellular proliferation, and further a reflection of arrest in G1 phase of the cell cycle and an increase in apoptosis [27]. Finally, this may lead to a reduction in the metastatic potential of the tumor [27, 29,30].

The likelihood of the implication of cetuximab in cancer therapy by additional anticancer mechanisms, such as inhibition of angiogenesis, has been demonstrated in human xenograft models, in which the impact of cetuximab on growth inhibition is often more pronounced than in cell culture [27]. Cetuximab has shown that inhibits the production of vascular endothelial growth factor (VEGF) in epidermoid carcinoma cells, which further causes a fall in the number of tumor blood vessels. Furthermore, it causes downregulation of interleukin-8 (IL-8) and the basic fibroblast growth factor (bFGF) expression, as well as the involution of tumor blood vessels and consequent inhibition of tumor growth.

The antimetastatic potential of cetuximab has also been demonstrated in mice with 253J B-V transitional cell carcinoma [31] and human prostate tumors [32]. Moreover, an ability to inhibit spontaneous metastasis in a severe combined immunodeficiency mouse xenograft model of metastatic melanoma may indicate an antibody-dependent cellular cytotoxicity response [33].

Preclinical research of cetuximab

Tumor cells depend on continued stimulation by growth factors [28]. As a result, an effective means of controlling tumor growth might be provided by the inhibition of the EGFR-signaling pathway. Indeed, the potential of cetuximab to modulate treatment outcome in SCCHN has been shown in *in vitro* and *in vivo* preclinical studies [34].

For example, it has been demonstrated that cetuximab enhances the antitumor effects of a variety of chemotherapeutic agents [28,35-39] and radiotherapy [29,40-42], or has its activity enhanced by them. Cetuximab has the ability to enhance the effects of radiation on human squamous cell carcinoma (SCC) tumor cell lines, as a result of the blockade of the EGFR signaling cascade, a fact demonstrated in *in vitro* studies [34,40, 43].

The effectiveness of cetuximab to improve tumor radio-response has also been established in SCC tumor xenografts in athymic mice [34,44]. Cetuximab is thought to exert its synergistic effects with radiotherapy at least partially, through strong inhibition of repairing damage in DNA, induced by radiation, in tumor cells [40]. The

improvement of local tumor control in preclinical studies by adding cetuximab in fractionated radiation therapy has been demonstrated by decreasing repopulation and increasing reoxygenation [45].

Based on these highly interesting and promising preclinical outcomes, it was a logical step to exploit the synergy between cetuximab and chemotherapy and radiotherapy and to investigate the effects of cetuximab in the clinical setting in the treatment of head and neck cancers [27,46].

Cetuximab plus radiotherapy in the treatment of locally advanced SCCHN

In patients with locally advanced SCCHN, cetuximab showed encouraging activity in an early study [47]. In this phase I trial, 16 patients with advanced SCCHN received cetuximab combined with conventional 70 Gy, 2 Gy/day or hyperfractionated 76.8 Gy, 1.2 Gy/twice a day radiotherapy. There was an impressive 100% response rate, since all patients achieved a major objective response (13 complete and 2 partial responses) and interestingly, both treatments were generally well tolerated.

Lately, the results of an international, multicentre phase III study, aiming to evaluate the combination of cetuximab with radiotherapy in 424 locally advanced head and neck cancer patients, have gained great scientific attention [48]. This randomized trial, reported by Bonner et al, is the first large-scale study that investigates the efficacy of combining a targeted agent with radiotherapy in this group of patients. The results showed that the addition of cetuximab to radiotherapy has significantly improved locoregional control and survival, opposite to radiotherapy alone.

Patients were stratified by Karnofsky performance status ([KPS] 90-100% vs. 60-80%), regional node involvement (positive vs. negative), tumor stage (T1-3 vs. T4) and radiation fractionation (concomitant boost vs. once-daily vs. twice-daily) and then randomized (1:1) to treatment with radiotherapy alone for 7-8 weeks (n = 213) or in combination with weekly-administered cetuximab (n = 211). The median age of patients in the radiotherapy and cetuximab plus radiotherapy groups was 58 and 56 years, respectively, and the majority were male. Most patients had a KPS of 90-100%, and the majority presented with oropharyngeal tumors. The treatment arms were well balanced with regard to patient and treatment characteristics.

The addition of cetuximab to radiotherapy significantly improved survival and locoregional control (defined as the absence of locoregional disease progression at the scheduled follow-up visits) compared with radiotherapy alone (Table 1).

Median overall survival with cetuximab plus radiotherapy was 49 months, almost 20 months longer than the one seen with radiotherapy alone (29.3 months; log-rank p=0.03). Similarly, there was a clear advantage for cetuximab plus radiotherapy over radiotherapy alone in the 3-year survival rate (55 vs. 45%, p=0.05). Cetuximab plus radiotherapy was therefore associated with a 26% risk reduction in mortality compared with radiotherapy alone (hazard ratio, HR: 0.74). The median duration of locoregional control after treatment with cetuximab plus radiotherapy was 9.5 months, longer than after radiotherapy alone (24.4 vs. 14.9 months; log-rank p = 0.005). There was also a clear advantage in the 3-year locoregional control rates ($p < 0.01$). Overall, cetuximab was associated with a 32% reduction in the risk of locoregional failure compared with radiotherapy alone (HR: 0.68). The above study showed that the addition of cetuximab to radiotherapy lead to convincing, statistically significant and clinically meaningful improvements in locoregional control, overall survival and progression-free survival. The value and quality of the data are supported by the fact that locoregional control was assessed in a blinded fashion by an independent clinical review committee. Additionally, it should be emphasized that with a group of more than

Table 1. Efficacy results of a phase III randomized trial comparing cetuximab plus radiotherapy with radiotherapy alone in patients with locally advanced SCCHN [48]

	Cetuximab plus radiotherapy (n=213)	*Radiotherapy alone (n=211)*	*Hazard ratio (95% CI)*	*p-value*
Median survival (months)	49.0	29.3	0.74 (0.57-0.97)	0.03
3-year survival (%)	55.0	45.0		0.05
Median locoregional control (months)	24.4	14.9	0.68 (0.52-0.89)	0.005
3-year locoregional control (%)	47.0	34.0		0.01
Median progression-free survival (months)	17.1	12.4	0.70 (0.54-0.90)	0.006
3-year progression-free survival (%)	42.0	31.0		0.04

n: number of patients, 95% CI: 95% confidence interval, SCCHN: squamous cell carcinoma of head and neck

420 patients, the Bonner study [48] is one of the largest ever performed in this setting.

Safety profile of cetuximab plus radiotherapy

Generally, cetuximab is well tolerated among patients. In the majority of them, an acne-like rash, characteristic of EGFR inhibitors, which is the most common side effect, was mild to moderate (grade 1-2). A special reference should be made for the cetuximab use in combination with radiotherapy (and/or chemotherapy). The findings of clinical studies in colorectal cancer and SCCHN show that cetuximab does not increase the side effects of chemotherapy or radiotherapy. These findings are supported by the data from the Bonner study, in which cetuximab did not statistically significantly increase the acute toxicities associated with radiotherapy, particularly mucous membrane disorders, radiation dermatitis and dysphagia, which were seen in similar numbers of patients in each arm. There was some additional toxicity that could be attributed to cetuximab, including grade 3-5 acne-like rash (17 vs. 1%) and a relatively greater incidence of grade 3-5 infusion reactions (3 vs. 0%).

Comparison of cetuximab plus radiotherapy with chemoradiotherapy

Actually, there are no controlled randomized trials comparing cetuximab plus radiotherapy with CRT. Nevertheless, to put the findings of the Bonner study into context with CRT, the results from the study can be viewed alongside those from a number of randomized studies involving more than 100 patients/ arm comparing CRT with radiotherapy in locally advanced disease (Table 2). Despite the fact that, such a comparison is

Table 2. Comparison of efficacy of different therapeutic regimens in published randomized phase III trials in patients with locally advanced head and neck cancer

Planned treatment		*Number of patients*	*3-year LRC %*	*3-year survival %*	*Median OS (months)*
Conventional RT [14,49]					
RT	Total 70 Gy, 2 Gy/day, 5 days/week	113	42	31	13
CRT	Same RT + carboplatin 70 mg/m^2/day+5-FU 600 mg/m^2/day on days 1-4,22-25, 43-46	109	66	51	20
Hyperfractionated RT [15]					
RT	Total median dose 74.4 Gy (72-76.8 Gy), 1.2 Gy twice daily over 7 weeks	112	40	50	29
CRT	same RT+ cisplatin 20 mg/m^2/day for 5 days in weeks 1+5	112	56	60	47
Hyperfractionated accelerated RT (concomitant boost) [50,51]					
RT	Total 69.9 Gy (38 days): 1.8 Gy/day, weeks 1-3; 1.8 + 1.5 Gy/day, weeks 4-5	127	38	30	16
CRT	Same RT with carboplatin 70 mg/m^2/day + 5-FU 600 mg/m^2/day on days 1-5, 29-33	113	50	40	23
RT [16]	Total 77.6 Gy (40 days): 14 Gy (2 Gy/day) then 1.4 Gy twice daily	194	39.2	28.6	16
CRT	Total RT 70.6 Gy (40 days): 30 Gy (2 Gy/day) then 1.4 Gy twice daily +mitomycin 10 mg/m^2 days 5 and 36 + 5-FU 600 mg/m^2 over days 1-5	190	51.8	37.5	23
Accelerated RT with breaks [4]					
RT	Total 70.2 Gy (51 days): 1.8 Gy twice daily in 3 courses (23.4 Gy/course)	140	17	24	16
CRT	Same RT + cisplatin 60 mg/m^2 on days 2, 22, 44 and 5- FU 350 mg/m^2/day + FA 50 mg/m^2/day on days 2-5, 22-25, 44-47	130	35	49	30
Cetuximab + radiotherapy [48]					
RT	6-7 weeks: once daily (70 Gy, 35 fractions), twice daily (72-76.8 Gy, 60-64 fractions), or concomitant boost (72 Gy, 42 fractions)	213	34	45	29.3
CRT	Same RT + cetuximab (1st dose 400 mg/m^2, 6 or 7 subsequent doses 250 mg/m^2/week)	211	47	55	49

CRT: chemotherapy combined with radiation therapy, FA: folinic acid, 5-FU: 5-fluorouracil, LRC: locoregional control, OS: overall survival, RT: radiotherapy

limited by differences in methodology and inconsistent definitions of locoregional control/failure, a number of observations can be made.

In this comparison, the results for the radiotherapy arm of the Bonner et al. study [48] were generally better than those seen in the radiotherapy arms of the CRT studies. The median overall survival times for CRT were better than for the corresponding radiotherapy groups alone in all CRT studies. Moreover, without an increase in clinically significant toxicities, the median survival with cetuximab plus radiotherapy in the Bonner study (49 months), was in the region of the upper and of the range of median survivals seen with CRT (20-47 months). Because of the difficulty in making direct comparisons of absolute survival values between studies, it is more significant to compare the increase in survival or survival time advantage within an individual study, given by the administration of chemotherapy or cetuximab over radiotherapy alone (median overall survival, Table 2). The median survival time advantage with adding chemotherapy to radiotherapy, which ranged from 7 to 18 months, was lower than that achieved by adding cetuximab to radiotherapy (nearly 20 months). Cetuximab appears to be highly effective in this setting. However, it does not significantly increase the toxicities, commonly associated with radiotherapy.

Discussion

When chemotherapy is available to patients with locally advanced SCCHN, the combined concomitant treatment, which consists of CRT, is nowadays considered as the standard approach. However, the increase in toxicity and poor compliance reported in studies with common use of CRT regimens, which is usually based on the use of cisplatin 100 mg/m^2 every 3 weeks for 3 cycles, limits the implementation of the approach on a larger scale for that patient group. In order to improve the patients' quality of life, the optimization of CRT strategies should focus on the trade-off between treatment efficacy and tolerability to treatment. The addition of novel, biologically-oriented therapies to radiotherapy may significantly improve the outcome of patients with locally advanced SCCHN. Compared with radiotherapy alone, the combinations of the EGFR inhibitor cetuximab and radiotherapy can decisively improve locoregional control and overall survival in locally advanced disease [48]. Moreover, the combination of cetuximab and radiotherapy appears to have efficacy benefits over radiotherapy alone, almost as great as those demonstrated with CRT, however without the associated toxicities.

The Bonner trial [48] unambiguously defines the way for further prospective investigations that would confirm the efficacy of cetuximab, whatever the level of tumor resectability. Such studies should perhaps attempt to identify subgroups of patients with the highest response to cetuximab-containing regimens.

Obviously, the use of non-cytotoxic drugs is still in its infancy and, to optimize their clinical application, we'll have to answer a number of questions first. In particular, should we focus on EGFR pathways or will we have to target both EGFR and VEGF mitogenic signals? Answering this question is bound to require time since the magnitude of the effects yielded by mono-or multi-targeted therapies markedly varies with tumor site: for instance, results observed in patients with colorectal cancer can not be extrapolated to those presenting with head and neck carcinoma, and *vice versa*. Another appealing approach seems to be targeting other pathways in concomitance with cytotoxic drugs and /or radiation. Recently, a number of genes have been identified, allowing extensive communication between insulin-like growth factor-1 (IGF-1), p53 and mammalian target of rapamycin (mTOR) pathways. In turn, the development of new agents designed to target various steps of c-Myc, Ras, and IGF cascade, as well as very recent advances in the identification of novel inhibitors, and also antisense oligonucleotides (ASOs) and siRNA, will herald extensive clinical programs that will help investigators know more about the safety and effectiveness of non-cytotoxic, targeted therapies, both as single agents or in combination with chemotherapy, radiation or CRT.

As a conclusion, in the treatment of locally advanced SCCHN, the combination of cetuximab and radiation therapy leads to significant benefits over radiotherapy alone. This combination could represent the indication of choice in patients presenting with intermediate-risk disease, for whom the satisfactory locoregional control rates do not justify the use of toxic CRT regimens. In patients with high- or very high-risk SCCHN, not amenable to chemotherapy or likely to show poor treatment compliance, this combination may also provide an effective and well tolerated alternative to CRT.

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