[Frontiers in Bioscience S3, 454-466, January 1, 2011]

Advances in EGFR-directed therapy in head and neck cancer

Gianmauro Numico[1], Nicola Silvestris[2], Elvio Grazioso Russi[3]

[1]SC Oncologia; Azienda USL della Valle d'Aosta, Aosta, Italy,[2]Medical and Experimental Oncology Unit, Istituto Oncologico, Bari, Italy, [3]SC Radioterapia Oncologica, A.O. S. Croce e Carle, Cuneo, Italy

TABLE OF CONTENTS

1. ABSTRACT

Initial research showed that EGFR targeting through known single agents, both monoclonal antibodies and small-molecule tyrosine-kinase inhibitors, applied to patients with refractory head and neck cancer, resulted in low response rates and short median survival times. However, the combination of Cetuximab with radiotherapy in patients with locally advanced disease and with a combination of platinum and fluorouracil in the setting of relapsed and/or metastatic disease resulted in a sharp improvement compared to standard therapy. Cetuximab entered clinical practice in both indications. Other anti-EGFR drugs, although showing activity, have not demonstrated an improvement of the results of standard therapy. Unfortunately, no molecular parameter emerged as a useful tool in predicting activity, thus impairing clinical applications. Only skin rash was repeatedly shown to be related with drug activity. Although generally well tolerated, class and drug specific toxicities can be troublesome and require knowledge and expertise for an optimal management. Further research is needed in order to find the best ways of integrating the anti-EGFR strategy with current standards of care.

2. INTRODUCTION

Head and neck cancer (HNC) is characterized by the tendency to loco-regional growth, while distant spread is usually a late event. This is the main reason of its high curability when it occurs in an initial stage. Almost one third of patients with HNC can be treated by radical excision and have a long-term survival rate of more than 80%. In another 50% of the cases, however, loco-regional spread can be controlled by demolitive surgery, aggressive chemoradiotherapy (CRT) regimens or both. Although at the cost of functional impairment and serious acute and late toxic effects, long-term survival is still 50%. In the unresectable or marginally resectable patients, standard therapy is the combination of full dose radiation therapy and chemotherapy. Although a reference regimen has not been established, the most utilized regimens consist of Cisplatin alone or a Cisplatin-based combination administered concurrently with radiotherapy. These treatments achieve complete response rates in the order of 60% and rates of 3-year survival of 50%. More recently induction chemotherapy with a three-drug combination achieved similar results and can be considered a valid alternative to concurrent regimens (1)(2)(3).

Table 1. Anti-EGFR agents undergoing active clinical research

Drug	Description	Phase of study
Cetuximab	Monoclonal antibody	Registered
Panitumumab	Monoclonal antibody	Phase III
Zalutumumab	Monoclonal antibody	Phase III
Nimotuzumab	Monoclonal antibody	Phase I-II
Gefitinib	EGFR- TKI	Phase III
Erlotinib	EGFR-TKI	Phase III
Lapatinib	EGFR and HER-2 – TKI	Phase III
BIBW 2992	EGFR and HER-2 – TKI	Phase II
Vandetanib	EGFR and VEGF – TKI	Phase II

Table 2. Trials assessing Cetuximab in the treatment of relapsed and/or metastatic HNC

Author	N.	Treatment	Previous CT	RR	Median PFS (months)	Median S (months)
Herbst(11)	126	P + Cetuximab	P-based CT	13%	3,0	6,1
Baselga (12)	96	P or Cb + Cetuximab	P-based CT	10%	2,8	6,2
Bourhis(76)	53	P/Cb + FU + Cetuximab	No	36%	5,0 (TTP)	10,0
Hitt(49)	42	Paclitaxel (weekly) + Cetuximab	No	60%	5,0 (TTP)	Nr
Knoedler(77)	47	Docetaxel + Cetuximab	P-based CT	20%	Nr	Nr
Burtness(13)	117	P + Placebo	No	10%	2,7	8,0
		P + Cetuximab	No	26%	4,0	9,2

CT: Chemotherapy; RR: response rate; PFS: Progression-free survival; S: Survival; TTP: Time to Progression; Nr: Not Reported; P: Cisplatin; Cb: Carboplatin

Approximately 10 to 20% of the patients develop distant metastatic disease: in these cases systemic treatment is the only active option but the aim is only a temporary palliation of symptoms. Also loco-regional relapses after radical treatment and second primaries are common causes of treatment failure and portend a dismal prognosis. Failures after loco-regional treatment are usually treated with palliative chemotherapy and share the same long-term prognosis of metastatic disease. Cisplatin-based chemotherapy yields response rates in the order of 20-40%, median progression-free survival times of 2 to 5 months and median survival times of 4-8 months. Unfortunately, no regimen resulted in improved survival in the context of randomized trials.

In patients with loco-regional relapse after surgery and/or radiation re-irradiation can be an option. Studies assessing the administration of full dose radiation concurrently with radiosensitising drugs showed an higher rate of objective responses in comparison with chemotherapy alone, although no demonstration of a survival benefit was achieved.

Thus, while HNC is an highly curable disease, improvement of both local and systemic treatments is a desirable end-point of current research. A further field of active work is the control of toxicities related to aggressive CRT regimens.

Drugs targeting the Epidermal Growth Factor Receptor (EGFR) have repeatedly shown activity in the treatment of HNC. Activity is probably driven by the inhibition of EGFR-mediated signaling and the consequent inhibition of cell proliferation (4)(5)(6)(7)(8). The property of enhancement of radiation effect has been demonstrated in preclinical trials. Mechanisms of synergistic activity include: reduction in the proportion of cells in the radioresistant S phase through G0/G1 cell cycle arrest, inhibition of repair of radiation-induced DNA damage, and induction of apoptosis.

Anti-EGFR agents have shown activity both in the treatment of relapsed/metastatic disease and in combination with radiotherapy in the treatment of locally advanced disease. Of the drugs that have been challenged in the treatment of HNC monoclonal antibodies are directed against the extracellular domain of EGFR and exert their action through inhibition of receptor dimerization and activation. Small-molecules tirosyne kinase inhibitors (TKI) bind to the ATP pocket of the receptor and block signaling to the cascade of intracellular messagers. Drugs inhibiting both HER-1 (EGFR) and HER2 have demonstrated activity in breast cancer and are undergoing active investigation also in HNC. Antisense oligonucleotides are small pieces of DNA coding for sequences that inhibit translation of EGFR m-RNA. They are introduced in the cell by a viral vector. This strategy is also being investigated due to its promising activity (Table 1).

The monoclonal antibody cetuximab is the only anti-EGFR agent currently approved for use in the treatment of HNC, based on studies demonstrating improved survival both in the loco-regional and in the metastatic setting.

3. CLINICAL APPLICATIONS OF ANTI-EGFR AGENTS

3.1. Cetuximab

Cetuximab is a chimeric, human:murine antibody of the IgG1 class, targeting the extracellular domain of the EGFR, with intrinsic antitumor activity (9). When assessed as single agent in the treatment of patients with chemotherapy-pretreated HNC a response rate of 13% was reported, together with an overall clinical benefit of 46%. Median Progression-Free Survival (PFS) was 2,3 months and median overall survival 6,0 months (10).

The preclinical demonstration of synergistic activity with platinum agents was the base of several phase II trials assessing the use of Cetuximab in combination with Cisplatin or Carboplatin in pretreated patients. (Table 2).

Cetuximab was shown to be active in patients refractory to platinum-based chemotherapy when combined to the same regimen with the aim of reversing resistance. Response rates in the range of 10 to 13% were reported and median PFS times of 3 months (11)(12).

Although no direct comparison is available, the activity of these regimens seems equivalent to the administration of Cetuximab as single agent in patients with platinum-refractory disease.

The demonstration of antitumoral activity in the pretreated population was preliminary to the assessment of the drug in the first line setting. A landmark randomized trial of the Eastern Cooperative Oncology Group (ECOG 53797) compared the combination of Cisplatin and Cetuximab with Cisplatin plus placebo in 117 patients with chemotherapy-free recurrent and/or metastatic HNC (13). The primary end point was PFS. Crossover to Cetuximab was allowed, thus masking the effect of the experimental regimen on overall survival. The dose of Cetuximab employed was lower than in other trials (200 mg/m^2 in the first administration and 125 mg/m^2 in the subsequent weekly doses). Cisplatin was given at the dose of 100 mg/m^2 every 4 weeks. PFS was improved in the Cetuximab arm (4,2 versus 2,7 months) although the difference did not reach statistical significance. Median survival was comparable between the two arms (9,2 versus 8,0 months). The trial showed a statistically significantly improved response rate (26% versus 10%, p: 0,03). Activity of the combination arm seemed to be higher in patients with skin rash and in those with low EGFR expression. These data provided the demonstration of the antitumor activity of EGFR targeting and opened the way to further research.

The EXTREME trial (Erbitux in first-line Treatment of Recurrent and Metastatic head and neck cancer) was a multicenter randomized, phase III trial conducted by the European Organization for Research and Treatment of Cancer (EORTC) investigators, with the aim of assessing the survival benefit of adding Cetuximab to a chemotherapy regimen consisting of Cisplatin (100 mg/m^2 day 1) or Carboplatin (AUC x 5, day 1) and Fluorouracil (1 g/m^2/day as a continuous infusion days 1-4) (14). Cetuximab was administered at the conventional doses of 450 mg/m^2 in the first infusion and 200 mg/m^2 at the subsequent ones. Anti-EGFR treatment was continued in non-progressing patients after the end of chemotherapy. 442 patients were randomized. The trial achieved its primary end point, demonstrating an overall survival for the experimental arm of 10,1 months compared with 7,4 months for the control arm (HR 0,80; p: 0,036). Response rates were 36% and 20% (p<0,001) and median PFS 5,6 and 3,3 months (p<0,001) respectively. The multivariate analysis suggested that the benefit of Cetuximab administration was limited to the younger and patients with good Performance Status (PS), those treated with Cisplatin combination (with respect to Carboplatin), oral cavity and well/moderately well differentiated tumors. The experimental treatment caused more frequent grade 3-4 skin rash (9% versus 1%), hypomagnesemia (5% versus 1%) and sepsis (4% versus <1%), although other typical chemotherapy-related toxicities were not worsened. The assessment of quality of life at cycle 3 and 6, a secondary end point of the trial, showed that the addition of Cetuximab did not affect overall quality of life. Moreover, symptoms as scored by the QLQ-H&N35 module of the EORTC scale showed improvement of social eating problems, speech problems, swallowing and pain (15). The EXTREME trial, being the first trial demonstrating a survival advantage in patients with relapsed/metastatic HNC, supported the registration of the triple drug combination as standard treatment.

After a dose-finding study showed the feasibility of combination of Cetuximab and radiation in 16 patients with locally advanced HNC (16), a large, international phase III trial compared radiotherapy alone with radiotherapy + Cetuximab, administered to patients with oropharyngeal, laryngeal or hypopharyngeal primaries (17). The primary end point was loco-regional control. The radiotherapy regimen could be selected among three schedules: once-daily, standard fractionated regimen; twice-daily; concomitant-boost. At a median follow up of 34 months the experimental arm had an improved median survival (49 versus 29 months, p: 0,03) and 3-year survival rate (55% versus 45%, p: 0,05) compared with radiation alone. An updated analysis confirmed the benefit in terms of survival, with a 5-year survival rate of 45,6% versus 36,4% (HR:0,73, p: 0,018) (18).

The analysis of disease recurrences showed that Cetuximab improved loco-regional control while did not influence the occurrence of distant metastases, suggesting that its principal role is the enhancement of radiation effect, being systemic cytoxicity probably limited.

Another important finding of the trial was toxicity. For the first time in the history of CRT protocols, the enhancement of antitumor effect did not parallel an enhancement of toxicity: actually, the combined regimen did not worsen local nor distant toxicities: acute grade 3 to 5 mucositis was reported to be 52% in the radiotherapy only arm and 56% in the combined treatment arm, dysphagia in 30% and 26% respectively; severe late radiotherapy-related adverse effects were reported to be in the order of 20% in both arms.

It must be noted, however, that Cetuximab led to some expected, drug-specific side effects (generalized skin rash, hypomagnesemia and hypersensitivity reactions) and to a largely unexpected local toxicity (infield skin toxicity). Although in the Bonner trial the radiation induced dermatitis was not reported as a problematic event, subsequent reports showed that this is a troublesome and frequent toxic effect of the combination of Cetuximab and radiation (19) (20) (21).

Unfortunately some weakness of the trial design limit the applicability of this regimen. First of all, the comparison with a non-standard control arm (radiotherapy alone) caused the prevalent inclusion of patients with “not-so-advanced” disease, so that the performance of the control arm was better than studies of CRT. Moreover, no

conclusions can be driven about the role of Cetuximab + RT with respect to the standard regimens of platinum-based CRT. This observation led many critics to consider the combination regimen still experimental and to encourage a direct comparison with CRT. The heterogeneity of the utilized radiotherapy regimens is another point that limits the application of this regimen into clinical practice: standard fractionated radiation and altered fractionated regimens can result in different acute and late toxicities. Notably, the rate of grade 3-4 mucositis (56%), is comparable with that of most common CRT combinations.

So, the commonly reported comment that the Cetuximab plus radiation regimen should be applied to elderly or unfit patients in which a classic CRT is contraindicated is debatable (22): although the Bonner trial provided a crucial proof of principle of the activity of Cetuximab further research is needed in order to clarify the unmet questions.

One application of the findings of these trials was inclusion of Cetuximab into CRT regimens, given the encouraging low toxic profile. In a randomized phase II trial, following an induction regimen with Cisplatin, Docetaxel and Fluorouracil, 115 patients with laryngeal or hypopharyngeal cancer were treated with concomitant Cisplatin and radiation or Cetuximab with the same radiation regimen (23). The treatment aim was larynx preservation. Preliminary results showed a similar rate of larynx preservation at 3 months after treatment (93% and 96% respectively) with a lower rate of toxic events and treatment interruptions in the Cetuximab arm. A phase II trial enrolling 22 patients assessed the combination of Cetuximab with a regimen consisting of Cisplatin and concomitant radiation using a concomitant boost technique (24). This trial was closed early due to excessive toxicity. The toxicity reported was mostly represented by infections and cardiovascular complications, leading to 2 deaths. The ECOG 3303 trial investigated the addition of Cetuximab to conventionally fractionated radiotherapy and Cisplatin at 75 mg/m^2 every 3 weeks for 3 times during radiation (25). Cetuximab was started 2 weeks before CRT and given as maintenance therapy for up to 6 months. Among 65 assessable patients one death due to febrile neutropenia was reported, together with multiple grade 4 adverse events including mucositis, nephrotoxicity, radiation dermatitis, fatigue. In a recently reported phase I dose-escalation trial, Cetuximab was associated to weekly Cisplatin and hyperfractionated-accelerated radiation in 18 patients. No dose limiting toxicity was found with increasing the Cisplatin dose up to 40 mg/m^2/week and the toxicity appeared predictable and manageable. One occurrence of gastric perforation was reported, together with one severe hypersensitivity reaction and one case of grade 4 neutropenia leading to death (26). A further study combined Cetuximab with simultaneous integrated boost, intensity modulated radiation plus Fluorouracil and Hydroxyurea. Among 33 patients no grade 4-5 adverse events were reported, suggesting that the optimization of local treatment may result in lower toxicity of the entire regimen (27). Our group recently terminated the AlteRCC trial (Alternating Radiotherapy and Chemotherapy combined with Cetuximab) with the combination of Cetuximab and an alternating CRT regimen (28). Toxicity seemed increased compared with the original alternating CRT regimen: grade 3-4 stomatitis occurred in 65% of the patients and 58% underwent prolonged enteral or parenteral feeding. Radiodermitis occurred in all patients and needed specific local measures. Three deaths were recorded during treatment (2 due to pneumonia and one to acute hearth failure).

The activity of these combined regimens are promising: an high number of complete responses is usually described and high figures of long term disease-free survival. However results are still preliminary, the contribution of Cetuximab is unclear and long term results must be evaluated with longer follow up. The combination with CRT must still be considered experimental and adopted only in the context of clinical trials. An RTOG randomized trial (RTOG 0522) is comparing accelerated radiation and Cisplatin with accelerated radiation, Cisplatin and Cetuximab. A similar trial, conducted by the Groupe Oncologie Radiotherapie Tete et Cou (GORTEC 2007- 01 trial), compares concurrent CRT plus Cetuximab with radiotherapy plus Cetuximab. The results of these trials will provide informations about the role of the addition of targeted therapy to the best control arm.

3.2. Panitumumab

Panitumumab is a fully humanized monoclonal antibody of the class of IgG2, binding to the extracellular domain of EGFR with high affinity. Compared to Cetuximab has a lower potential of inducing hypersensitivity reactions, has a longer half-life and a higher affinity for EGFR.

A phase I trial assessed the combination of Panitumumab with increasing weekly doses of Paclitaxel, Carboplatin concurrent with intensity-modulated radiation. Among 19 patients, 18 achieved clinical complete response, although local grade 3-4 toxicity was frequent. Grade 3 radiation dermatitis occurred in 42% (29). Phase III trials are ongoing both in the locally advanced and in the relapsed/metastatic setting.

3.3. Zalutumumab

In a phase III trial enrolling 286 patients with locally advanced or metastatic HNC pretreated with platinum-based chemotherapy, Zalutumumab, an IgG1 completely human anti-EGFR monoclonal antibody, administered as intravenous infusion every 2 weeks at the starting dose of 4 mg/Kg and with a dose-escalation scheme aiming at reaching skin rash, was compared with best supportive care. In the control arm the use of single-agent Methotrexate was permitted and was actually given in the majority of the patients. The response rate of the experimental arm was 6%, the median PFS was 9,9 weeks and the median survival was 6,7 months. These figures were better than those of the control arm, although the difference in median survival did not reach statistical significance. This study suggest that Zalutumumab has promising activity in platinum-refractory disease, that seems comparable with Cetuximab (30). A phase III trial

Table 3. Trials assessing Gefitinib in relapsed and/or metastatic HNC

Author	N.	Previous CT	RR	Median PFS (months)	Median S (months)
Cohen*(78)	52	yes	10,6%	3.4	8.1
Wheeler(79)	32	yes (12)	15%	3.0	6.0
Cohen**(80)	70	yes	1.4%	1.8	5.5
Kirby*(81)	47	yes	8%	2,6	3,4
Stewart**(33)	158	yes	2.7%	Nr	5,6
Stewart*(33)	167	Yes	7,6%	Nr	6,0

* 500 mg/day; **250 mg/day, CT: chemotherapy; RR: Response Rate; PFS: Progression-free Survival; S: Survival; Nr: Not reported

of the Danish Head and Neck Cancer Group (DAHANCA 19) is ongoing comparing the combination of Zalutumumab and radiotherapy with treatment including concurrent CRT.

Other anti-EGFR monoclonal antibodies which are in clinical research are Matuzumab (EMD72000) and Nimotuzumab (H-R3) (31). Nimotuzumab, when tested in combination with radiotherapy, showed promising activity and a low degree of skin rash (32)

3.4. Gefitinib

The application of single-agent Gefitinib to patients with pretreated recurrent/metastatic HNC did demonstrate activity, with response rates in the range of 1 to 11%, although median PFS and survival did not appear different from historical data. One notable finding was that trials assessing the dose of 500 mg/day had higher response rates than trials assessing the standard dose of 250 mg/day (Table 3). The drug is well tolerated with main toxicities consisting in grade 1-2 skin rash in 48% of the patients, grade 1-2 diarrhea in 42% of the patients and grade 3 in 6%.

An international randomized phase III trial enrolling 486 pretreated patients compared Methotrexate with Gefitinib at the dose of 250 mg/day and 500 mg/day, with survival improvement as primary end point. The trial confirmed the higher activity of the 500 mg dose over the 250 mg (response rate: 7,6% versus 2,7%). However, it failed to show any significant difference in terms of activity or efficacy with respect to the control arm (33).

A recently reported phase III trial compared weekly Docetaxel with or without Gefitinib 250 mg daily, in patients with PS 2 and or pretreated HNC. The trial closed after accrual of 270 patients due to an interim analysis suggesting that the primary end point of demonstrating an overall survival difference between arms was not reached. The reported median survival time was 6 month in the control arm and 6,8 in the experimental one. However, both response rate (6% versus 14%) and median time to progression (2 versus 3,5 months) favored the combination arm (34) .

The combination with radiation has been tested in a phase I, dose-escalation trial. Gefitinib was administered on a daily basis at the dose of 250 mg or 500 mg in combination with a concomitant-boost radiation schedule. In the second part of the trial the 500 mg dose was given in the context of a CRT regimen in which radiation was given along with weekly Cisplatin (30 mg/m^2). Gefitinib was then continued after the end of radiation at the dose of 250 mg daily as maintenance therapy up to 2 years. The trial suggested the feasibility of the combination, with a low rate of toxic events: grade 3-4 dermatitis occurred in 13% of the patients; grade 1-2 skin rash occurred in 78%, grade 3-4 stomatitis in 57%, grade 3-4 diarrhea in 17% (35). These data suggest that Gefitinib does not increase the toxicities expected to occur with altered fractionated regimen and CRT combinations.

In a phase II trial, after induction chemotherapy with Carboplatin and Paclitaxel, Gefitinib was given with Fluorouracil, Hydroxyurea, and twice daily radiation. Gefitinib was continued thereafter for 2 years. In 56 evaluable subjects a complete response rate of 91% was achieved, with an overall survival of 73% at 3 years (36).

3.5. Erlotinib

Erlotinib hydrochloride (Erlotinib, Tarceva, OSI Pharmaceuticals, New York, NY) is an orally available, potent, reversible, and selective EGFR inhibitor.

In a phase II trial 115 patients with recurrent/metastatic HNC (35% pretreated with palliative chemotherapy) were given Erlotinib 150 mg orally on a daily basis. The overall response rate was 4,3%, and 38,3% of the treated patients had stable disease. Median PFS was 9,6 weeks, median survival was 6 months and the 1-year survival rate was 20%. Toxicity was generally mild: rash and diarrhea occurred in 79% and 37% of the patients, respectively. Eleven percent of patients experienced grade 3-4 skin rash and grade 3 diarrhea occurred in four patients (3%) (37).

Two other phase II trials employed Erlotinib in the context of polichemotherapy, in first line recurrent/metastatic disease. After a phase I dose-escalation study, Canadian researchers enrolled 44 patients in a phase II trial in which patients were treated with Cisplatin 75 mg/m^2 every 21 days and Erlotinib 100 mg daily. The response rate was 21%, median PFS rate 3,3 months, median survival 7,9 months, 1-year survival 19,5% (38). In the other trial 47 evaluable patients with HNC who had not received chemotherapy for relapsed/metastatic disease were treated with Docetaxel 75 mg/m^2 , Cisplatin 75 mg/m^2 intravenously every 3 weeks and Erlotinib 150 mg daily. Response rate was 67%, median PFS 6 months and median overall survival 11 months (39). A single study assessed Erlotinib monotherapy in the neoadjuvant setting. Among 31 evaluable patients receiving Erlotinib 150 mg/day before undergoing surgery, the response rate was 29% and

stable disease 60%, with only one patient progressing during treatment (40). In a phase I/II trial combining Erlotinib and Bevacizumab in patients with refractory HNC, this regimen showed a 14% rate of objective response, 54% rate of disease stability, a median PFS of 3,8 months, and a median survival 6,8 months. The simultaneous action on the EGFR pathway and the VEGF pathway was demonstrated feasible and potentially promising (41).

As a general comment the results obtained by Erlotinib are close to what is seen with Gefitinib, with variations mainly due to the inclusion criteria of the trials. In particular the inclusion of patients with refractory disease lowers the response rates of second-line agents. Conversely, treatment of non-pretreated patients and combination with active drugs, mainly Cisplatin, are ways of increasing the response rate.

In summary, EGFR TKIs are active drugs in HNC and activity seems not so different from that of Cetuximab. Objective response rates are in the range of 1% to 10%, with disease stabilization rates of 33% to 47%, median PFS from 1.8. to 3.4. months and median survival from 5.5. to 8.1. months. Patients in these studies typically were heavily pretreated, with 59% to 85% having had prior exposure to chemotherapy. Unfortunately, no demonstration is available that they are also able to influence the natural history of the disease, as was shown with Cetuximab.

3.6. Other TKI

Lapatinib is a dual kinase, reversible TKI, targeting both EGFR and HER2. These two receptors, when activated, dimerize to form functional signaling complexes. Combined targeting of HER2 and EGFR may result in enhanced clinical responses compared to EGFR-targeted therapies alone. In a single-arm phase II trial Lapatinib was administered to 42 patients with relapsed/metastatic disease already pretreated with chemotherapy. Unfortunately no responses occurred, while disease stabilization was obtained in 37% and median PFS was 1,6 months (42).

Lapatinib was recently assessed in the context of a CRT regimen. In a phase II randomized trial Lapatinib, administered as induction, concomitant and adjuvant treatment showed encouraging results in terms of complete response rates, PFS and overall survival (43).

Other dual TKI undergoing investigation are BIBW 2992 (EGFR + HER2 TKI) and Vandetanib (EGFR + VEGF TKI).

3.7. Other treatment strategies

Another approach of EGFR inhibition was the development of an antisense EGFR oligonucleotide, with the aim of blocking the EGFR protein coding. In a study conducted by researchers of the University of Pittsburgh, the sequence, inserted into the plasmide of a viral vector, was injected in accessible tumor mass weekly for 4 times. Among 17 patients with advanced, refractory disease, two complete and three partial responses were achieved, for an overall response rate of 29%. Disease stabilization was obtained in another 41%. Median survival was 5,4 months in the overall population but was 7,9 in the responding patients (44). Although these results are encouraging the response was shown to be strictly dependent on the tumor diameter, with small masses being favorite targets; moreover, not all site of disease could be reached, limiting the generalizability of the results.

4. WHICH PATIENT BENEFITS?

Although both monoclonal antibodies and TKI have a clear target (EGFR) that is largely expressed in HNC, to date the search of clinical or biological features predicting sensitivity or resistance to EGFR inhibitors has been discouraging.

Immunohistochemical expression of EGFR was the most studied tool, being directly referable to the functional pathway of protein synthesis and externalization on the cell membrane. Moreover, immunohistochemical expression has been related to the aggressiveness of cancer and radioresistance (45)(46). Unfortunately, there is no evidence that the level of expression is predictive of anti-EGFR activity. In the ECOG 5397 trial assessing the role of Cetuximab in combination with Cisplatin in the relapsed/metastatic setting, a relation between anti-EGFR activity and immunohistochemical staining for EGFR was searched for. A counterintuitive finding of this trial was that tumors with the highest expression (evaluated as intensity and density – 3+ and >80% of the cells) had lower response rates to Cetuximab (13). Also in the Bonner trial, in a subgroup analysis, expression of EGFR in more than 50% of the cells was related with lower efficacy of the combination of Cetuximab and radiation, compared to cases with lower expression (17). No impact of this parameter on the activity of anti-EGFR therapies was found also with Erlotinib in the relapsed/metastatic patients (37). The high variability of the technical processes used to detect EGFR together with the subjective interpretation of expression, prevent solid conclusions to be made.

Amplification of the EGFR gene, as detected by Fluorescence in-situ hybridization (FISH), was found to correlate with higher response rates, PFS and overall survival in 31 patients treated with Erlotinib and Cisplatin (47). In the randomized trial comparing Gefitinib with Methotrexate in patients with recurrent/metastatic disease the incidence of FISH-positive tumors was approximately 40%. Median survival was not different between treatment arms in FISH-positive and negative patients, although the response rates seemed to be increased in FISH-positive patients undergoing treatment with higher Gefitinib doses (500 mg, 13,8%) compared with lower doses (250 mg, 3,6%) and with chemotherapy (0%) (33). On the other hand, FISH testing was not found to be a predictive factor in the analysis of the EXTREME trial, comparing a platinum based chemotherapy with the same plus Cetuximab (48). Similar results were obtained in a trial assessing the combination of Cetuximab and Paclitaxel in patient with relapsed/metastatic disease (49).

Activating somatic mutations of the EGFR gene are rare in HNC. On the contrary EGFRvIII has been reported to be frequent and potentially related to anti-EGFR activity. EGFRvIII is a truncated form of EGFR resulting from deletion of exons 2 to 7 of the EGFR gene. The resulting protein, lacking the ligand-binding domain, is constitutively activated and is not responsive to the inhibitory activity of anti-EGFR molecules. EGFRvIII is expressed in 40% of HNC and is a potential marker of resistance to both monoclonal antibodies and TKI (6).

While biologically parameters substantially failed in highlighting response or resistance to anti-EGFR therapies, a clinical manifestation of treatment such as skin rash was repeatedly related with antitumor activity of these agents. In the ECOG 5397 trial (13) patients treated with Cisplatin and Cetuximab and facing skin rash of any grade had a lower risk of death than those without skin toxicity. Also response rate was significantly better in patients with skin toxicity than in the counterpart (33% versus 7%). Similar data were shown in a phase II study testing the activity of Cetuximab and Cisplatin in platinum-refractory patients (11). In the Bonner trial, patients treated with Cetuximab and radiotherapy complaining a "prominent" rash (grade 2-4) had a statistically significant longer overall survival than patients with a "mild" rash (grade 0-1) (18). The same relation between skin rash and activity was not demonstrated in other trials such as the EXTREME trial. A relation between skin rash and clinical benefit was found also in TKI trials. In the phase II trials assessing Erlotinib both as single agent and with Cisplatin in recurrent/metastatic HNC median survival was significantly related with intensity of skin rash (no skin rash: 4,0 months, grade 1, 5,0 months, and grade 2-4, 7,4 months) (37)(38).

5. TOXICITY OF ANTI-EGFR AGENTS

Although anti-EGFR agents do not share the toxic effects of cytotoxics, clinical trials showed that toxicity should be an item when considering their use.

A first point is the enhancement of the typical chemotherapy-related toxicities. Although this has not been shown for TKI, there is some evidence that the combination of Cetuximab with chemotherapy worsens some of the typical toxicities of cytotoxics. For example in the ECOG 5397 trial, the combination of Cetuximab and Cisplatin caused more grade 3-4 neutropenia (30% versus 14%) and thrombocytopenia (11% versus 4%) than Cisplatin alone (13). In the EXTREME trial, although the hematological effects were equivalent, an increased incidence of septic complications was found in the Cetuximab arm (14). A higher degree of hematological toxicities was shown also in trials assessing the addition of Cetuximab in treatment regimens for other disease such as lung cancer (50).

The other point is the occurrence of class-specific toxicities: generalized skin rash and low-grade diarrhea are common to all anti-EGFR agents while hypomagnesemia, hypersensitivity reactions and radiodermitis have been demonstrated with monoclonal antibodies.

5.1. Skin rash

The use of EGFR targeting agents is associated with frequent dermatological toxicities: papulo-pustular rash, skin dryness, desquamation, pruritus and paronychia. Skin toxicity occurs within the first two weeks and can evolve into infection and ulceration when treatment is not withdrawn.

The papulo-pustular eruption consists of erythematous follicular papules that evolve into pustules. Lesions may coalesce to form plaques covered by pustules and form crusty lesions. The eruption usually involves the scalp, face, neck, shoulders, and upper trunk.

The events underlying skin toxicities are anti-EGFR induced keratinocytes dysfunction and apoptosis, follicular inflammation, abnormal keratinization of the epidermidis and bacterial superinfection. In addition, the EGFR pathway has a major impact on the inflammatory/immune reactions of the skin, in the apparent effort both of enhancing innate immune defence and of opposing to the over-activation of pro-inflammatory functions of the keratinocytes. So, EGFR inhibitors, cause skin inflammation and favour microbial colonization and superinfection (51) (52) (53) .

Rash seems slightly more frequent with monoclonal antibodies (Cetuximab and Panitumumab, 90%) than with TKI (Gefitinib and Erlotinib, 70%). A meta-analysis of the studies employing Cetuximab found, among 2037 patients, an overall incidence of skin rash of 88%, with 11% being grade 3-4 (54).

Skin rash is typically reversible with drug withdrawal. However, strategies directed to an effective management have been pursued in order to prevent a reduction in clinical activity through excessive alterations of the treatment regimen. A randomized study from the North Central Cancer Treatment Group compared oral Tetracycline with placebo in the prevention of skin toxicity from EGFR inhibitors. Among the 61 patients enrolled a clear effect on the incidence of rash was not evident although some improvement in physician-reported toxicity and patient-reported quality of life was shown (55). In a phase III trial, the prophylactic administration of minocycline decreased the severity of papulo-pustular rash. Minocycline is an antibiotic of the class of tetracycline with anti-inflammatory properties through effects on lymphocytes proliferation, neutrophils chemotaxis, up-regulation of Interleukine 10 and inhibition of Interleukine 6 production. At the oral dose of 100 mg/day beginning from the first day of Cetuximab administration, patients had a lower mean facial lesion count at the peak of the rash, and fewer patients complained moderate to severe itch and rash compared to patients receiving placebo (56). In a randomized phase II trial enrolling patients with colorectal cancer treated with Panitumumab, a pre-emptive therapy beginning the day before treatment start was effective in reducing the incidence of grade 2 or more skin rash. The skin treatment consisted of skin moisturizer applied every morning, sunscreen, topical hydrocortisone applied at bedtime, and Doxycycline taken at the dose of 100 mg

twice daily. In the pre-emptive arm grade 2 or more toxicity was 29% compared with 62% in the arm in which treatment was instituted at the time of toxicity occurrence (57).

5.2. Radiation dermatitis

Skin injury is a well-known effect of radiation. It results from the inhibition of epidermal cell repopulation, recruitment of inflammatory cells in the dermal space, microvascular leakage and thrombosis (58). The cells in the basal and suprabasal layers of the epidermis are rapidly killed and a repopulative, EGFR-driven response is simultaneously triggered (59). Erythema, dry desquamation, moist desquamation and skin necrosis with consequent ulceration and bleeding due to dermal exposure are the clinical counterparts of the pathological, progressive injury.

The severity of clinical manifestations is strictly dependent on the equilibrium between apoptosis and proliferation of epidermal cells. Treatment intensity and particularly accelerated fractionation, reducing the necessary time for repopulation, increases this type of toxic effect. Another way of increasing skin damage is interference with repopulation through the administration of drugs such as cytotoxics and anti-EGFR agents. The EGFR system has an important role in epidermal repair and in the skin response to damaging agents. Damage to epidermal integrity triggers activation of a EGFR-mediated system that leads to proliferation, protection from apoptosis, cell adhesion and migration, anti-inflammatory activity that ultimately promote repair of the damaged skin (58). EGFR blockade induces a dysregulation in expression of genes implied in defensive mechanisms and finally causes inhibition of proliferation in basal cells and hair follicles, susceptibility to apoptosis, inhibition of cell migration, induction of inflammation. The histological counterpart is thinning of corneum stratum, parakeratosis, thinning and interruption of the granular cell layer (60). From a clinical point of view, this damage causes skin drying and diffuse xerosis, thinning of the functional strata, inflammatory reaction and folliculitis (61) (62) (19) (63).

In the Bonner trial a non-significant 5% difference in radiation dermatitis between the two arms was shown (18% in the radiotherapy arm and 23% in the Cetuximab plus radiotherapy arm) (17). However, in subsequent case reports and clinical series this toxicity emerged as a troublesome event, occurring in more than 50% of patients in its severe form (20) (64). Giro *et al.* reported on findings from a survey with an analysis of 71 patients treated with Cetuximab and radiotherapy, 50% of whom developed grade 3 or more radiation dermatitis (65). In a trial of combined Cetuximab, Cisplatin, Fluorouracil and radiation, Merlano *et al.* found an incidence of 74% of grade 3 radiation dermatitis among 45 patients (66). These figures support the conclusion that this toxicity is frequent in its most severe form and potentially impairs treatment compliance.

It was also soon demonstrated that the adoption of general preventive measures, together with timely and appropriate management of radiodermitis could result in maximal reduction of the impact on patients quality of life and rapid complete resolution. Preventive measures consist of avoidance of sun exposure and use of sunscreen, avoidance of harsh detergents and skin irritants, use of warm water and bath oils to keep the irradiated region clean; use of topical moisturizers, minimization of trauma by friction and protection of the irradiated area with soft clothing (67).

When xerosis become evident, debridement of crusts is recommended, using hydrogels emollients and subsequent gentle, manual debridement. The desquamated areas must be protected with occlusive-dressing (polyuretane) or burn-dressing (hydrocolloids or hydrofibres). A correct management of radiodermitis causes pain relief, reduces the risk of infection and ultimately allows adherence to treatment (21).

5.3. Hypersensitivity reactions

Hypersensitivity reactions are common consequences of intravenous infusions of proteins such as monoclonal antibodies. These reactions are reported to be frequent in their minor manifestations (20 to 30%), but rarely they can be severe and potentially lethal. The occurrence of severe reactions to Cetuximab is reported to be 3% while is below 1% for Panitumumab, a fully humanized antibody. The development of hypersensitivity reactions challenges clinicians in treatment continuation and may prevent patients to be treated with an effective regimen, both in the locally advanced and in the recurrent/metastatic setting.

The physiopathologic mechanism underlying reactions to Cetuximab seems IgE mediated, that is true drug-mediated anaphylaxis. A murine carbohydrate moiety of the monoclonal antibody is identified by IgE and the presence of serum IgE antibody reacting with Cetuximab has been reported to be predictive of hypersensitivity (68).

Routine premedication with antihistamines is considered mandatory before Cetuximab administration, while is not indicated before Panitumumab. In a large post hoc analysis performed on patients with colorectal cancer, the addition of corticosteroids significantly reduced the incidence of reactions (from 25,6% to 9,6%) (69) (70). Being reactions limited mostly to the first infusion the administration of a test dose has been suggested with the purpose of cost saving, while an impact on the severity of the reactions has not been shown. The management of the reaction should be immediate and previously established through written center-specific protocol interventions. Nurse monitoring should prompt immediate interruption of the infusion and activation of general supportive measures in the case of even suspected reaction. Rechallenge after a previous non-severe reaction can be attempted using a complete premedication (consisting of both H1 and H2 antihistamines plus corticosteroids), while a severe reaction imposes treatment withdrawal (71).

5.4. Hypomagnesemia

Hypomagnesemia is a typical Cetuximab-related effect. EGFR has been found in the tubular cells of the

glomerular collecting tubules involved in Mg^{2+} reabsorption. Blockade of EGFR causes abnormal urinary excretion and reduction of Mg^{2+} circulating levels. Mg^{2+} deficiency (plasma concentrations below 1,5 mg/dL) impairs muscle physiology and causes tetany, prolonged QT interval, cardiac arrhythmias and/or convulsions. In patients with history of cardiovascular disease hypomagnesemia is a risk factor for severe consequences. The occurrence of severe hypomagnesemia is estimated to be in the order of 10% to 15% of the treated patients, although a decrease in the serum concentrations of magnesium is almost universal (72) (73) and the incidence seems directly related to the duration of Cetuximab treatment. The combined administration of drugs impairing magnesium tubule reabsorption such as Cisplatin and aminoglycosides and other causes of renal impairment such as diabetic nephropathy and sepsis can contribute to severe magnesium depletion.

Secondary hypocalcemia, with symptoms of fatigue, muscle cramps and tetany, is a possible consequence of magnesium deficit and responds to magnesium supplementation. While hypomagnesemia is caused also by Panitumumab, this is not the case for the TKI Gefitinib and Erlotinib. Monitoring of Mg levels is required every 2 to 4 weeks during anti-EGFR treatment. Oral supplementation can be offered in case of grade 1 toxicity (1,5 -1,2 mg/dL) or when treatment with Cetuximab or Panitumumab is discontinued. Magnesium supplementation is indicated in case of grade 2 hypomagnesemia (1,2 – 0,9 mg/dL), when the patient has cardiac risk factors and always in case of grade 3-4 (below 0,9 mg/dL). For patients with grade 2 hypomagnesemia, weekly intravenous replacement (4 g of magnesium sulfate) is preferred, being the oral administration less effective and poorly tolerated (due to diarrhea). In case of grade 3-4, daily supplementation is required, as serum magnesium levels tend to lower within 3–4 days after the weekly administration. Some authors suggest 6–10 g of magnesium sulfate daily to twice weekly (74). An initial strategy of IV replacement and every-other-day serum magnesium monitoring is helpful to guide the frequency of replacement until a steady state is reached. The possibility of a temporary withdrawal of anti-EGFR treatment should always be considered, as hypomagnesemia is rapidly reversible.

5.5. Interstitial Lung Disease (ILD)

Both Gefitinib and Erlotinib have been implicated in cases of severe and even fatal ILD. In lung cancer studies both agents where involved in the occurrence of ILD, the main risk factor being an Asian origin. In HNC studies this toxicity was assessed in the trial comparing Gefitinib with Methotrexate in the relapsed/metastatic setting. ILD events were reported with a frequency of approximately 1% without significant differences between the 250 mg dose, the 500 mg dose and the Methotrexate arm (33).

The low number of patients with HNC entered in clinical trials and treated with TKI prevent against definite conclusion about the occurrence of ILD. The involvement of Cetuximab and other monoclonal antibodies is uncertain. A clear relationship with ILD is certainly less evident than in the case of TKI (75).

6. PERSPECTIVES

Targeting EGFR has been a successful strategy in the treatment of HNC. All drugs demonstrated clinical activity, although only Cetuximab entered routine clinical practice due to the statistically significant advantage in overall survival when added to standard therapy both in the locally advanced setting and in the relapsed/metastatic setting. The combination of anti-EGFR agents with current treatment regimens is favoured by the toxicity profile. However, some toxic effect should be acknowledged and correctly managed in order to spare the patient from serious adverse events and provide optimal treatment. Unfortunately no definitive predictive criteria of benefit is available, except for skin rash. Further research should find biological tools useful in selecting the more sensitive patients for treatment with anti-EGFR drugs. New agents and new targets are under active study and will offer new opportunities for treatment of HNC.

7. REFERENCES

1. Haddad RI, Shin DM. Recent Advances in Head and Neck Cancer. *N Engl J Med* 359(11):1143-1154 (2008)

2. Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. *Lancet* 371: 1695-1709 (2008)

3. Choong N, Vokes E. Expanding role of the medical oncologist in the management of head and neck cancer. *CA Cancer J Clin* 58 :32-53 (2008)

4. Kim S, Grandis JR, Rinaldo A, Takes RP, Ferlito A. Emerging perspectives in epidermal growth factor receptor targeting in head and neck cancer. *Head Neck* 30: 667-674 (2008)

5. Brockstein B, Lacouture M, Agulnik M. The role of inhibitors of the epidermal growth factor in management of head and neck cancer. *J Natl Compr Canc Netw* 6 :696-706 (2008)

6. Harari PM, Wheeler DL, Grandis JR. Molecular target approaches in head and neck cancer: epidermal growth factor receptor and beyond. *Semin Radiat Oncol* 19: 63-68 (2009)

7. Egloff AM, Grandis JR. Targeting epidermal growth factor receptor and SRC pathways in head and neck cancer. *Semin. Oncol* 35 :286-297 (2008)

8. Gold KA, Lee H, Kim ES. Targeted therapies in squamous cell carcinoma of the head and neck. *Cancer* 115: 922-935 (2009)

9. Mehra R, Cohen RB, Burtness BA. The role of cetuximab for the treatment of squamous cell carcinoma of the head and neck. *Clin Adv Hematol Oncol* 6: 742-750 (2008)

10. Vermorken JB, Trigo J, Hitt R, Koralewski P, Diaz-Rubio E, Rolland F, Knecht R, Amellal N, Schueler A, Baselga J. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. *J Clin Oncol* 25: 2171-2177 (2007)

11. Herbst RS, Arquette M, Shin DM, Dicke K, Vokes EE, Azarnia N, Hong WK, Kies MS. Phase II Multicenter Study of the Epidermal Growth Factor Receptor Antibody Cetuximab and Cisplatin for Recurrent and Refractory Squamous Cell Carcinoma of the Head and Neck. *J Clin Oncol* 23: 5578-5587 (2005)

12. Baselga J, Trigo JM, Bourhis J, Tortochaux J, Cortes-Funes H, Hitt R, Gascon P, Amellal N, Harstrick A, Eckardt A. Phase II Multicenter Study of the Antiepidermal Growth Factor Receptor Monoclonal Antibody Cetuximab in Combination With Platinum-Based Chemotherapy in Patients With Platinum-Refractory Metastatic and/or Recurrent Squamous Cell Carcinoma of the Head and Neck. *J Clin Oncol* 23: 5568-5577 (2005)

13. Burtness B, Goldwasser MA, Flood W, Mattar B, Forastiere AA. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. *J Clin. Oncol* 23: 8646-8654 (2005)

14. Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, Rottey S, Erfan J, Zabolotnyy D, Kienzer H, Cupissol D, Peyrade F, Benasso M, Vynnychenko I, De Raucourt D, Bokemeyer C, Schueler A, Amellal N, Hitt R. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med* 359: 1116-1127 (2008)

15. Mesía R, Rivera F, Kawecki A, Rottey S, Hitt R, Kienzer H, Cupissol D, De Raucourt D, Benasso M, Koralewski P, Delord J, Bokemeyer C, Curran D, Gross A, Vermorken JB. Quality of life of patients receiving platinum-based chemotherapy plus cetuximab first line for recurrent and/or metastatic squamous cell carcinoma of the head and neck [Internet]. *Ann Oncol* [cited 2010 Giu 28]

16. Robert F, Ezekiel MP, Spencer SA, Meredith RF, Bonner JA, Khazaeli MB, Saleh MN, Carey D, LoBuglio AF, Wheeler RH, Cooper MR, Waksal HW. Phase I Study of Anti-Epidermal Growth Factor Receptor Antibody Cetuximab in Combination With Radiation Therapy in Patients With Advanced Head and Neck Cancer. *J Clin Oncol* 19: 3234-3243 (2001)

17. Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB, Jones CU, Sur R, Raben D, Jassem J, Ove R, Kies MS, Baselga J, Youssoufian H, Amellal N, Rowinsky EK, Ang KK. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 354: 567-578 (2006)

18. Bonner JA, Harari PM, Giralt J, Cohen RB, Jones CU, Sur RK, Raben D, Baselga J, Spencer SA, Zhu J, Youssoufian H, Rowinsky EK, Ang KK. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol* 11: 21-28 (2010)

19. Berger B, Belka C. Severe skin reaction secondary to concomitant radiotherapy plus cetuximab. *Radiat Oncol* 3: 5 (2008)

20. Budach W, Bölke E, Homey B. Severe cutaneous reaction during radiation therapy with concurrent cetuximab. *N Engl J Med* 357: 514-515 (2007)

21. Russi EG, Merlano MC, Comino A, Numico G. Ultrathin hydrocolloid dressing in skin damaged from alternating radiotherapy and chemotherapy plus cetuximab in advanced head and neck cancer (G.O.N.O. AlteRCC Italian Trial): in regard to Macmillan *et al.* (Int J Radiat Oncol Biol Phys 2007;68:864-872). *Int J Radiat Oncol Biol Phys* 69: 638-639 (2007)

22. Bernier J, Schneider D. Cetuximab combined with radiotherapy: an alternative to chemoradiotherapy for patients with locally advanced squamous cell carcinomas of the head and neck? *Eur J Cancer* 43: 35-45 (2007)

23. Lefebvre J, Pointreau Y, Rolland F, Alfonsi M, Baudoux A, Sire C, de Raucourt D, Bardet E, Tuchais C, Calais G, Groupe Oncologie Radiotherapie Tete Et Cou (GORTEC). Sequential chemoradiotherapy (SCRT) for larynx preservation (LP): Preliminary results of the randomized phase II TREMPLIN study. *J Clin Oncol* (Meeting Abstracts) 27(15S): 6010 (2009)

24. Pfister DG, Su YB, Kraus DH, Wolden SL, Lis E, Aliff TB, Zahalsky AJ, Lake S, Needle MN, Shaha AR, Shah JP, Zelefsky MJ. Concurrent cetuximab, cisplatin, and concomitant boost radiotherapy for locoregionally advanced, squamous cell head and neck cancer: a pilot phase II study of a new combined-modality paradigm. *J Clin Oncol* 24: 1072-1078 (2006)

25. Langer CJ, Lee JW, Patel UA, Shin DM, Argiris AE, Quon H, Ridge JA, Forastiere AA. Preliminary analysis of ECOG 3303: Concurrent radiation (RT), cisplatin (DDP) and cetuximab (C) in unresectable, locally advanced (LA) squamous cell carcinoma of the head and neck (SCCHN). *J Clin Oncol* (Meeting Abstracts) 26 (15S): 6006 (2008)

26. Kuhnt T, Sandner A, Wendt T, Engenhart-Cabillic R, Lammering G, Flentje M, Grabenbauer G, Schreiber A, Pirnasch A, Dunst J. Phase I trial of dose-escalated cisplatin with concomitant cetuximab and hyperfractionated-accelerated radiotherapy in locally advanced squamous cell carcinoma of the head and neck [Internet]. *Ann Oncol* [cited 2010 Giu 29] Available from: http://www.ncbi.nlm.nih.gov.bvs.cilea.it/pubmed/20427347 (2010)

27. Kao J, Policarpio L, Teng M, Burri R, Genden E, Packer S. Phase II trial of concurrent 5-fluorouracil, hydroxyurea, cetuximab, and intensity modulated radiation therapy (IMRT) for locally advanced head and neck cancer. *J Clin Oncol* (Meeting Abstracts) 27(15S): 6014 (2009)

28. Merlano M. Alternating chemotherapy and radiotherapy in locally advanced head and neck cancer: an alternative? *Oncologist* 11(2): 146-151 (2006)

29. Wirth LJ, Allen AM, Posner MR, Haddad RI, Li Y, Clark JR, Busse PM, Chan AW, Goguen LA, Norris CM, Annino DJ, Tishler RB. Phase I dose-finding study of paclitaxel with panitumumab, carboplatin and intensity-modulated radiotherapy in patients with locally advanced squamous cell cancer of the head and neck. *Ann Oncol* 21: 342-347 (2010)

30. Machiels JH, Subramanian S, Ruzsa A, Repassy G, Lifrenko I, Flygare A, Sorensen P, Ehrnrooth E, Baadsgaard O, Clement PM. An open-label, randomized, phase III trial of zalutumumab, a human monoclonal EGF receptor (EGFr) antibody, versus best supportive care, in patients with noncurable squamous cell carcinoma (SCCHN) of the head and neck who have failed standard platinum-based chemotherapy (ZALUTE). *J Clin Oncol* (Meeting Abstracts) 28(18S):LBA5506 (2010)

31. Rojo F, Gracias E, Villena N, Cruz T, Corominas JM, Corradino I, Cedeño M, Campas C, Osorio M, Iznaga N, Bellosillo B, Rovira A, Marsoni S, Gascon P, Serrano S, Sessa C, Crombet T, Albanell J. Pharmacodynamic trial of nimotuzumab in unresectable squamous cell carcinoma of the head and neck: a SENDO Foundation study. *Clin Cancer Res* 16: 2474-2482 (2010)

32. Rodríguez MO, Rivero TC, del Castillo Bahi R, Muchuli CR, Bilbao MA, Vinageras EN, Alert J, Galainena JJ, Rodríguez E, Gracias E, Mulén B, Wilkinson B, de Armas EL, Pérez K, Pineda I, Frómeta M, Leonard I, Mullens V, Viada C, Luaces P, Torres O, Iznaga N, Crombet T. Nimotuzumab plus radiotherapy for unresectable squamous-cell carcinoma of the head and neck. *Cancer Biol Ther* 9: 343-349 (2010)

33. Stewart JSW, Cohen EEW, Licitra L, Van Herpen CML, Khorprasert C, Soulieres D, Vodvarka P, Rischin D, Garin AM, Hirsch FR, Varella-Garcia M, Ghiorghiu S, Hargreaves L, Armour A, Speake G, Swaisland A, Vokes EE. Phase III study of gefitinib compared with intravenous methotrexate for recurrent squamous cell carcinoma of the head and neck [corrected]. *J Clin Oncol* 27: 1864-1871 (2009)

34. Argiris A, Ghebremichael M, Gilbert J, Burtness B, Forastiere A. A phase III randomized, placebo-controlled trial of docetaxel (D) with or without gefitinib (G) in recurrent or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN): A trial of the Eastern Cooperative Oncology Group (ECOG). *J Clin Oncol* (Meeting Abstracts) 27(15S): 6011 (2009)

35. Chen C, Kane M, Song J, Campana J, Raben A, Hu K, Harrison L, Quon H, Dancey J, Baron A, Said S, Eckhardt SG, Raben D. Phase I trial of gefitinib in combination with radiation or chemoradiation for patients with locally advanced squamous cell head and neck cancer. *J Clin Oncol* 25: 4880-4886 (2007)

36. Ahmed SM, Cohen EE, Haraf DJ, Stenson KM, Blair E, Brockstein BE, Lin S, Lester E, Dekker A, Williams R, Vokes EE. Updated results of a phase II trial integrating gefitinib (G) into concurrent chemoradiation (CRT) followed by G adjuvant therapy for locally advanced head and neck cancer (HNC). *J Clin Oncol* (Meeting Abstracts) 25(18S): 6028 (2007)

37. Soulieres D, Senzer NN, Vokes EE, Hidalgo M, Agarwala SS, Siu LL. Multicenter phase II study of erlotinib, an oral epidermal growth factor receptor tyrosine kinase inhibitor, in patients with recurrent or metastatic squamous cell cancer of the head and neck. *J Clin Oncol* 22: 77-85 (2004)

38. Siu LL, Soulieres D, Chen EX, Pond GR, Chin SF, Francis P, Harvey L, Klein M, Zhang W, Dancey J, Eisenhauer EA, Winquist E. Phase I/II trial of erlotinib and cisplatin in patients with recurrent or metastatic squamous cell carcinoma of the head and neck: a Princess Margaret Hospital phase II consortium and National Cancer Institute of Canada Clinical Trials Group Study. *J Clin Oncol* 25: 2178-2183 (2007)

39. Kim ES, Kies MS, Glisson BS, Tsao A, Ginsberg LE, Holsinger FC, Burke BJ, Truong M, Papadimitrakopoulou VA, Lippman SM. Final results of a phase II study of erlotinib, docetaxel and cisplatin in patients with recurrent/metastatic head and neck cancer. *J Clin Oncol* (Meeting Abstracts) 25 (18S): 6013 (2007)

40. Thomas F, Rochaix P, Benlyazid A, Sarini J, Rives M, Lefebvre JL, Allal BC, Courbon F, Chatelut E, Delord J. Pilot study of neoadjuvant treatment with erlotinib in nonmetastatic head and neck squamous cell carcinoma. *Clin Cancer Res* 13:7086-7092 (2007)

41. Vokes EE, Cohen EEW, Mauer AM, Karrison TG, Wong SJ, Skoog-Sluman LJ, Kozloff MF, Dancey J, Dekker A. A phase I study of erlotinib and bevacizumab for recurrent or metastatic squamous cell carcinoma of the head and neck (HNC). *J Clin Oncol* (Meeting Abstracts) 23 (16S): 5504 (2005)

42. Abidoye OO, Cohen EE, Wong SJ, Kozloff MF, Nattam SR, Stenson KM, Blair EA, Day S, Dancey JE, Vokes EE. A phase II study of lapatinib (GW572016) in recurrent/metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN). *J Clin Oncol* (Meeting Abstracts) 24 (18S): 5568 (2006)

43. Harrington KJ, Berrier A, Robinson M, Remenar E, Housset M, Hurtado de Mendoza F, Compton N, Lau M, Legenne P, Kumar R. Phase II study of oral lapatinib, a dual-tyrosine kinase inhibitor, combined with chemoradiotherapy (CRT) in patients (pts) with locally advanced, unresected squamous cell carcinoma of the head

and neck (SCCHN). *J Clin Oncol* (Meeting Abstracts) 28 (15S): 5505 (2010)

44. Lai SY, Koppikar P, Thomas SM, Childs EE, Egloff AM, Seethala RR, Branstetter BF, Gooding WE, Muthukrishnan A, Mountz JM, Lui VWY, Shin DM, Agarwala SS, Johnson R, Couture LA, Myers EN, Johnson JT, Mills G, Argiris A, Grandis JR. Intratumoral epidermal growth factor receptor antisense DNA therapy in head and neck cancer: first human application and potential antitumor mechanisms. *J Clin Oncol* 27: 1235-1242 (2009)

45. Ang KK, Berkey BA, Tu X, Zhang H, Katz R, Hammond EH, Fu KK, Milas L. Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck carcinoma. *Cancer Res* 62: 7350-7356 (2002)

46. Numico G, Russi EG, Colantonio I, Lantermo RA, Silvestris N, Vitiello R, Comino A, Abrate M, Zavattero C, Melano A, Merlano M. EGFR status and prognosis of patients with locally advanced head and neck cancer treated with chemoradiotherapy. *Anticancer Res* 30: 671-676 (2010)

47. Agulnik M, da Cunha Santos G, Hedley D, Nicklee T, Dos Reis PP, Ho J, Pond GR, Chen H, Chen S, Shyr Y, Winquist E, Soulieres D, Chen EX, Squire JA, Marrano P, Kamel-Reid S, Dancey J, Siu LL, Tsao MS. Predictive and pharmacodynamic biomarker studies in tumor and skin tissue samples of patients with recurrent or metastatic squamous cell carcinoma of the head and neck treated with erlotinib. *J Clin Oncol* 25: 2184-2190 (2007)

48. Licitra L, Rolland F, Bokemeyer C, Remenar E, Kienzer H, Stoerkel S, Scheid S, Stroh C, Mesia R. Biomarker potential of EGFR gene copy number by FISH in the phase III EXTREME study: Platinum-based CT plus cetuximab in first-line R/M SCCHN. *J Clin Oncol* (Meeting Abstracts) 27 (15S): 6005 (2009)

49. Hitt R, Martín P, Hidalgo M. Cetuximab in squamous cell carcinoma of the head and neck. *Future Oncol* 2: 449-457 (2006)

50. Pirker R, Pereira JR, Szczesna A, von Pawel J, Krzakowski M, Ramlau R, Vynnychenko I, Park K, Yu C, Ganul V, Roh J, Bajetta E, O'Byrne K, de Marinis F, Eberhardt W, Goddemeier T, Emig M, Gatzemeier U. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. *Lancet* 373: 1525-1531 (2009)

51. Lacouture ME, Cotliar J, Mitchell EP. Clinical management of EGFRI dermatologic toxicities: US perspective. *Oncology* (Williston Park, N.Y.) 21 (11 Suppl 5): 17-21 (2007)

52. Pastore S, Mascia F, Mariani V, Girolomoni G. The epidermal growth factor receptor system in skin repair and inflammation. *J Invest Dermatol* 128: 1365-1374 (2008)

53. Jatoi A, Rowland K, Sloan JA, Gross HM, Fishkin PA, Kahanic SP, Novotny PJ, Schaefer PL, Johnson DB, Tschetter LK, Loprinzi CL. Tetracycline to prevent epidermal growth factor receptor inhibitor-induced skin rashes: results of a placebo-controlled trial from the North Central Cancer Treatment Group (N03CB). *Cancer* 113: 847-853 (2008)

54. Su X, Lacouture ME, Jia Y, Wu S. Risk of high-grade skin rash in cancer patients treated with Cetuximab - an antibody against epidermal growth factor receptor: systemic review and meta-analysis. *Oncology* 77: 124-133 (2009)

55. Jatoi A, Rowland K, Sloan JA, Gross HM, Fishkin PA, Kahanic SP, Novotny PJ, Schaefer PL, Johnson DB, Tschetter LK, Loprinzi CL. Tetracycline to prevent epidermal growth factor receptor inhibitor-induced skin rashes: results of a placebo-controlled trial from the North Central Cancer Treatment Group (N03CB). *Cancer* 113: 847-853 (2008)

56. Scope A, Agero ALC, Dusza SW, Myskowski PL, Lieb JA, Saltz L, Kemeny NE, Halpern AC. Randomized double-blind trial of prophylactic oral minocycline and topical tazarotene for cetuximab-associated acne-like eruption. *J Clin Oncol* 25: 5390-5396 (2007)

57. Lacouture ME, Mitchell EP, Piperdi B, Pillai MV, Shearer H, Iannotti N, Xu F, Yassine M. Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a pre-Emptive Skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. *J Clin Oncol* 28: 1351-1357 (2010)

58. Segaert S, Van Cutsem E. Clinical signs, pathophysiology and management of skin toxicity during therapy with epidermal growth factor receptor inhibitors. *Ann Oncol* 16: 1425-1433 (2005)

59. Dent P, Reardon DB, Park JS, Bowers G, Logsdon C, Valerie K, Schmidt-Ullrich R. Radiation-induced release of transforming growth factor alpha activates the epidermal growth factor receptor and mitogen-activated protein kinase pathway in carcinoma cells, leading to increased proliferation and protection from radiation-induced cell death. *Mol Biol Cell* 10: 2493-2506 (1999)

60. Russi EG, Merlano MC, Comino A, Numico G. Ultrathin hydrocolloid dressing in skin damaged from alternating radiotherapy and chemotherapy plus cetuximab in advanced head and neck cancer (G.O.N.O. AlteRCC Italian Trial): in regard to Macmillan *et al.* (Int J Radiat Oncol Biol Phys 2007;68:864-872). *Int J Radiat Oncol Biol Phys* 69: 638-639 (2007)

61. Agero ALC, Dusza SW, Benvenuto-Andrade C, Busam KJ, Myskowski P, Halpern AC. Dermatologic side effects associated with the epidermal growth factor receptor inhibitors. *J Am Acad Dermatol* 55: 657-670 (2006)

62. Hu JC, Sadeghi P, Pinter-Brown LC, Yashar S, Chiu MW. Cutaneous side effects of epidermal growth factor

receptor inhibitors: clinical presentation, pathogenesis, and management. *J Am Acad Dermatol* 56: 317-326 (2007)

63. Tejwani A, Wu S, Jia Y, Agulnik M, Millender L, Lacouture ME. Increased risk of high-grade dermatologic toxicities with radiation plus epidermal growth factor receptor inhibitor therapy. *Cancer* 115: 1286-1299 (2009)

64. Mydin AR, Armstrong JG. Acneiform rash secondary to cetuximab plus head and neck radiotherapy. *Radiother Oncol* 85: 171 (2007)

65. Giro C, Berger B, Bölke E, Ciernik IF, Duprez F, Locati L, Maillard S, Ozsahin M, Pfeffer R, Robertson AG, Langendijk JA, Budach W. High rate of severe radiation dermatitis during radiation therapy with concurrent cetuximab in head and neck cancer: results of a survey in EORTC institutes. *Radiother Oncol* 90: 166-171 (2009)

66. Merlano MC, Numico G, Russi EG, Benasso M, Colantonio I, Vigna Taglianti R, Lanzilotta L, Vigo V, Bacigalupo A. Cetuximab (C-mab) and chemo-radiation (CT-RT) for loco-regional advanced squamous cell carcinoma of the head and neck (HNC): A phase II study. *J Clin Oncol* (Meeting Abstracts) 25 (18S): 6043 (2007)

67. Bernier J, Bonner J, Vermorken JB, Bensadoun R, Dummer R, Giralt J, Kornek G, Hartley A, Mesia R, Robert C, Segaert S, Ang KK. Consensus guidelines for the management of radiation dermatitis and coexisting acne-like rash in patients receiving radiotherapy plus EGFR inhibitors for the treatment of squamous cell carcinoma of the head and neck. *Ann Oncol* 19: 142-149 (2008)

68. Chung CH, Mirakhur B, Chan E, Le Q, Berlin J, Morse M, Murphy BA, Satinover SM, Hosen J, Mauro D, Slebos RJ, Zhou Q, Gold D, Hatley T, Hicklin DJ, Platts-Mills TAE. Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. *N Engl J Med* 358: 1109-1117 (2008)

69. Siena S, Glynne-Jones R, Adenis A, Thaler J, Preusser P, Aguilar EA, Aapro MS, Loos AH, Esser R, Wilke H. Reduced incidence of infusion-related reactions in metastatic colorectal cancer during treatment with cetuximab plus irinotecan with combined corticosteroid and antihistamine premedication. *Cancer* 116: 1827-1837 (2010)

70. George TJ, Laplant KD, Walden EO, Davis AB, Riggs CE, Close JL, George SN, Lynch JW. Managing cetuximab hypersensitivity-infusion reactions: incidence, risk factors, prevention, and retreatment. *J Support Oncol* 8: 72-77 (2010)

71. Lenz H. Management and preparedness for infusion and hypersensitivity reactions. *Oncologist* 12: 601-609 (2007)

72. Tejpar S, Piessevaux H, Claes K, Piront P, Hoenderop JGJ, Verslype C, Van Cutsem E. Magnesium wasting associated with epidermal-growth-factor receptor-targeting antibodies in colorectal cancer: a prospective study. *Lancet Oncol* 8: 387-394 (2007)

73. Izzedine H, Bahleda R, Khayat D, Massard C, Magné N, Spano JP, Soria JC. Electrolyte disorders related to EGFR-targeting drugs. *Crit Rev Oncol Hematol* 73: 213-219 (2010)

74. Fakih M. Anti-EGFR monoclonal antibody-induced hypomagnesaemia. *Lancet Oncol* 8: 366-367 (2007)

75. Hoag JB, Azizi A, Doherty TJ, Lu J, Willis RE, Lund ME. Association of cetuximab with adverse pulmonary events in cancer patients: a comprehensive review. *J Exp Clin Cancer Res* 28:113 (2009)

76. Bourhis J, Rivera F, Mesia R, Awada A, Geoffrois L, Borel C, Humblet Y, Lopez-Pousa A, Hitt R, Vega Villegas ME, Duck L, Rosine D, Amellal N, Schueler A, Harstrick A. Phase I/II study of cetuximab in combination with cisplatin or carboplatin and fluorouracil in patients with recurrent or metastatic squamous cell carcinoma of the head and neck. *J Clin Oncol* 24: 2866-2872 (2006)

77. Knoedler MK, Gauler T, Matzdorff A, Jordan O, Schroeder M, Gruenwald V, Dietz A, Arnold D, Hennemann B, Keilholz U. Multicenter phase II study of cetuximab plus docetaxel in 84 patients with recurrent or metastatic, platinum-pretreated SCCHN. *J Clin Oncol* (Meeting Abstracts) 27 (15S): 6048 (2009)

78. Cohen EEW, Rosen F, Stadler WM, Recant W, Stenson K, Huo D, Vokes EE. Phase II trial of ZD1839 in recurrent or metastatic squamous cell carcinoma of the head and neck. *J Clin Oncol* 21: 1980-1987 (2003)

79. Wheeler RH, Jones D, Sharma P, Davis RK, Spilker H, Boucher K, Leachman S, Grossman D, Salzman K, Akerley W. Clinical and molecular phase II study of gefitinib in patients (pts) with recurrent squamous cell cancer of the head and neck (H&N Ca). *J Clin Oncol* (Meeting Abstracts) 23 (16S): 5531 (2005)

80. Cohen EEW, Kane MA, List MA, Brockstein BE, Mehrotra B, Huo D, Mauer AM, Pierce C, Dekker A, Vokes EE. Phase II trial of gefitinib 250 mg daily in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. *Clin Cancer Res* 11: 8418-8424 (2005)

81. Kirby AM, A'Hern RP, D'Ambrosio C, Tanay M, Syrigos KN, Rogers SJ, Box C, Eccles SA, Nutting CM, Harrington KJ. Gefitinib (ZD1839, Iressa) as palliative treatment in recurrent or metastatic head and neck cancer. *Br J Cancer* 94: 631-636 (2006)

Key Words: Head and neck Cancer, Chemoradiotherapy, EGFR, Review

Send correspondence to: Gianmauro Numico, SC Oncologia, Azienda USL della Valle d'Aosta, Viale Ginevra 3, 11100 Aosta, Tel 0165-543608, Fax: 0165-543622, E-mail: gnumico@ausl.vda.it