OPEN ACCESS Freely available online

doi:10.4172/1948-5956.1000005

Management of Cutaneous Toxicity and Radiation Dermatitis in Patients with Squamous Cancer of the Head and Neck Undergoing Concurrent Treatment with Cetuximab and Radiotherapy

Ricard Mesía*, Esther Vilajosana, Alicia Lozano, Laura Esteller, Vazquez Silvia

Institut Catala d'Oncologia, L'Hospitalet, Barcelona, SPAIN

Abstract

Review Article

Skin toxicity is the most common adverse event associated with the use of EGFR inhibitors. Radiation dermatitis occurs to some degree in most of the patients who receive radiotherapy, either alone or in combination with EGFR inhibitors. The effects of both toxicities might be additive because the irradiated skin zone in squamous cell cancer of the head and neck (SCCHN) patients is the same area in which the EGFR inhibitor-related acne-like rash is more common. This article summarizes the principal issues discussed during a symposium that took place in Madrid in January 2009, in which the management of cutaneous toxicity and radiation dermatitis in patients with SCCHN was reviewed. Selection of the most appropriate control measures was discussed in an interactive debate with the audience using five case reports.

It was concluded that early establishment of adequate preventive measures and proper management of both the EGFR inhibitor-related, acne-like rash and radiation dermatitis in SCCHN patients undergoing concomitant treatment will prevent treatment interruption, potentially allowing better locoregional control of the disease.

Keywords: Cetuximab; Skin toxicity; Radiotherapy; Skin toxicity management

Introduction

Head and neck cancers account for 6% of all cancers worldwide, with nearly 150,000 new cases in Europe alone each year (CANCERMondial). The distribution of primary tumor sites is: oral cavity (49%), pharynx (23%) and larynx (28%) (Parkin et al., 2002). Patients with recurrent, metastatic disease have a poor prognosis, with a median survival of around 6-7 months (Schantz et al., 2001). In addition, patients failing first-line therapy have few therapeutic options.

The epidermal growth factor receptor (EGFR) is expressed in nearly all squamous cell cancer of the head and neck (SCCHN) and carries a strong prognostic significance, providing the rationale for using EGFR-targeted agents, such as cetuximab (Erbitux[®]) in this indication, as shown in previous trials (Burtness, 2005; Bourhis et al., 2006).

Cetuximab in monotherapy as second line treatment in patients that have progressed to platinum has shown a 10% response rate and a 35% rate of stable disease (Vermorken et al., 2005a).

The phase III clinical trial conducted by Vermorken et al. (2008b) in which cetuximab was combined to conventional

chemotherapy (platinum/5-FU) in stage III/IV recurrent and/or metastatic SCCHN patients, not suitable for local therapy, was the first one in 30 years to show a survival benefit [median survival 7.4 months (chemotherapy alone) vs. 10.1 months (chemotherapy+cetuximab), p=0.036] over platinum-based chemotherapy. Adverse events were similar in both arms (anemia, neutropenia, thrombocytopenia), except for acne-like rash and infusion reactions in the cetuximab group.

The study by Bonner et al. (2006) also demonstrated that the combination of cetuximab to high-dose radiotherapy improved loco regional control and reduced mortality in locally advanced SCCHN patients, with a similar toxicity profile in general, only increasing the rate and the median duration of cutaneous toxicity but not the rate of radiation dermatitis.

The combination of cetuximab and weekly paclitaxel in patients with recurrent and/or metastatic SCCHN patients has also shown excellent results (60% OS, 88% DCR), with a similar toxicity profile, only increasing the acne-like rash, infusion reactions and conjunctivitis (Hitt et al., 2007).

New strategies that are currently being explored include multiples options with the addition of cetuximab as neo-adjuvant treatment, the administration of cetuximab maintenance therapy, as well as neoadjuvant treatment with docetaxel, cisplatin and 5-fluorouracil (TPF) combined with cetuximab in stage IV irresectable, locally advanced SCCHN patients (Mesía et al., 2008a).

Health Education Offered by the Nursing Staff to Patients that are Going to Receive Cetuximab Treatment in our Institution

The Medical Unit in our institution is formed by medical and radiation oncologists, fellows and a research nurse practitioner. The Unit has its own administrative system that allows a tight monitoring of ambulatory patients, reducing the need of hospitalizations and providing support for any disease related event including toxicity, psychosocial and nutritional issues.

*Corresponding author: Ricard Mesía, Institut Catala d'Oncologia, L'Hospitalet, Barcelona, SPAIN, E-mail: <u>rmesia@iconcologia.net</u>

Received October 22, 2009; Accepted November 23, 2009; Published November 24, 2009

Citation: Mesía R, Vilajosana E, Lozano A, Esteller L, Silvia V (2009) Management of Cutaneous Toxicity and Radiation Dermatitis in Patients with Squamous Cancer of the Head and Neck Undergoing Concurrent Treatment with Cetuximab and Radiotherapy. J Cancer Sci Ther 1: 028-033. doi:10.4172/1948-5956.1000005

Copyright: © 2009 Mesía R, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Citation: Mesía R, Vilajosana E, Lozano A, Esteller L, Silvia V (2009) Management of Cutaneous Toxicity and Radiation Dermatitis in Patients with Squamous Cancer of the Head and Neck Undergoing Concurrent Treatment with Cetuximab and Radiotherapy. J Cancer Sci Ther 1: 028-033. doi:10.4172/1948-5956.1000005

After the physician visit the research nurse provides the patient with information that describes the expected cutaneous toxicity associated with cetuximab treatment in combination with radiotherapy. During that visit a nurse form, adapted from Majorie Gordon's model that includes personal data, nutritional and psychosocial baseline evaluation of the patient is filled out. The weekly visit allows the evaluation of the appearance of early toxicity and whether psycho-social or nutritional support is required. The close follow up includes telephone calls in order to evaluate the need of analgesia, topical cures, undernourishment as well as other potential patient's needs.

Orobuccal and skin recommendations prior to treatment initiation

The orobuccal recommendations prior to treatment initiation include: 1)dental check up; b)while on treatment alcohol consumption and smoking should be avoided; c)rinsing of the oral cavity with thyme infusion and bicarbonate is recommended; d)brushing after every meal is also recommended as well as good hydration; e)administration of lidocaine gel (2%) for oral ulcer treatment.

The skin recommendations that should be initiated one week before treatment has started include: 1)daily wash of face and neck with warm water, avoiding the use of skin irritants such as soap, perfumes, deodorants or alcohol-based lotions; use soap substitutes such as avena lotion instead; maintain daily wash during the treatment, unless skin ulcerations appear; 2)apply body lotion cream daily in order to prevent and improve dry skin specially on treated area; 3)avoid hydrating lotions that contain aloe vera; 4)avoid hair dye; 5)avoid the use of razors; use electric shaving machines instead; 6)avoid the use of hot water in those skin areas affected; use warm water instead, 7)avoid scratching of the skin in the affected areas; 8)avoid sun exposure wherever possible.

Cutaneous Toxicity and Radiation Dermatitis: Clinical Characteristics and General Management

Clinical characteristics of skin toxicity

EGFR is expressed in the basal layer of the epidermis, and is known to be essential to the regulation of several aspects of normal keratinocyte biology. Effects of EGFR inhibition include impaired growth and migration of keratinocytes and inflammatory chemokine expression by these cells. These effects lead to inflammatory cell recruitment and subsequent cutaneous injury, which accounts for the majority of symptoms, including acneiform rash, xerosis, pruritus, hyperpigmentation, fissures in fingers and toes, hypertrichosis, periungual inflammation and onycholisis. The acneiform rash appears in those areas rich of sebaceous glands such as face, neck, retroauricular area, back, upper trunk, and the scalp. The most common clinical symptoms associated are: confluent pustules, diffuse erythema with telangiectasias or papulopustules, seborrheic dermatitis-like rash, edematous facial erythema. Histologic specimens reveal a mixed inflammatory infiltrate surrounding the upper areas of the dermis, follicular rupture, and epithelial acantholysis. Those areas are frequently the areas that undergo irradiation in SCHHN patients. In most of the cases, 85%, the skin toxicity is graded as grade I-II only, although this gradation is based on the body area affected

and the presence of other symptoms. The most important skin areas affected are face and neck areas when patients are treated with concomitant radiotherapy plus cetuximab. We prefer to classify the skin toxicity as "Severe" if there is a diffuse erythema, with confluent follicular papulopustules with yellowish drainage and severe oedema; "Moderate" if there moderate is erythema, pustules, pruritus, and oedema; and "Minor" if there is only mild edema, erythema and a few pustules.

Clinical characteristics of radiation dermatitis

Radiation dermatitis is experienced, to various degrees, by the majority of the SCCHN patients undergoing radiotherapy. Only 20 to 25% of the patients experience severe reactions. The incidence of the severe reactions depend on the total radiation dose, the dose per fraction, the overall treatment time, beam and energy type and the skin area exposed to radiation. The toxicity grading of radiation dermatitis, according to RTOG criteria, is as follows: Grade 0: no changes; grade 1: faint erythema or dry desquamation; grade 2: moderate to brisk erythema; patchy moist desquamation, severe oedema; Grade 3: confluent moist desquamation, severe oedema; Grade 4: ulceration, bleeding, skin necrosis.

The consequences of the appearance of radiation dermatitis include progressive, local discomfort, risk of infection; worsening of patient's quality of life and more important, can lead to delays in treatment administration that might compromise treatment efficacy.

The percentage of grade 3 radiation dermatitis in different randomized studies have ranged from 11% when conventional or accelerated radiotherapy with concomitant boost was used to 18% in non randomized studies that have used intensitymodulated radiation therapy (Bernier et al., 2008).

When combined to conventional chemotherapy, several studies have shown an important increase in radiation dermatitis (from 7-12% to 17-23%) (Brizel, 1998; Wendt, 1998; Calais, 1999; Jeremic, 2000; Adelstein, 2003; Huguenin, 2004). The phase III randomised trial conducted by Bonner et al. (2006) that compared radiotherapy with or without cetuximab revealed no statistically significant increase in the incidence or severity of radiation dermatitis (18% vs 23%, p = 0.027). However, a slight increase in the median duration of the radiation dermatitis was noted (11.1 weeks vs. 9.4 weeks).

The results of the study of Mesia et al., (2008a) showed that the addition of adjuvant treatment with cetuximab did not increase the radiation dermatitis toxicity. The addition of cisplatin to cetuximab and radiotherapy is not associated with an increase in radiation dermatitis (Pfister, 2006; Langer, 2008).

Management of cutaneous toxicity

Severe cutaneous toxicity: Cetuximab treatment should be suspended if necrotic or ulcerative confluent lesions appear. Topical treatment with mupirocin twice a day should be applied on the ulcers or suppurative or infected areas. The administration of an oral antibiotic [doxycycline (50-100 mg/day) or clindamicin (150 mg/8h)] should be considered. The ulcerated areas should not be humidified because it could prevent from healing. Patients should be monitored at least twice a week.

Journal of Cancer Science & Therapy - Open Access

Moderate cutaneous toxicity: Topical administration of corticoids is recommended (i.e. betametasone 0.05% twice a day, after radiotherapy or at night; treatment should not be administered beyond two weeks. Topical treatment with mupirocin twice a day should be applied on the ulcers or suppurative or infected areas. Pruritus responds well to sedating antihistamines such as ebastine (1 pill/day). The ulcerated areas should not be humidified because it could prevent from healing. Patients should be monitored once a week.

Mild cutaneous toxicity: Apply moisturising lotion the affected area. Topical antibiotics such as erythromycin or doxycycline should be applied, after radiotherapy or at night, on the acneiform rash in other to dry it out. Topical administration of corticoids on the erythematous/edematous areas is recommended (i.e. betametasone 0.05% twice a day, after radiotherapy or at night; treatment should not be administered beyond two weeks). Pruritus responds well to sedating antihistamines such as ebastine (1 pill/day). The ulcerated areas should not be humidified because it could prevent from healing.

Management of radiation dermatitis

Grade 1 radiation dermatitis: No specific treatment is required. Moisturizing of the affected area should be increased.

Grade 2-3 radiation dermatitis: The irradiated area should be kept clean and dry, even with the presence of ulcers. Moisturizing creams without alcohol are recommended. When a super infection is suspected the exudate should be cultivated and a topical antibiotic should be administered. In those cases with severe infections an oral antibiotic should be administered. Topical administration of corticoids on the inflamed areas is recommended (i.e. betametasone 0.05% twice a day, after radiotherapy or at night; treatment should not be administered beyond two weeks). Topical treatment with mupirocin twice a day should be applied on the ulcers or suppurative or infected areas. Patients should be monitored at least twice a week.

Grade 4 radiation dermatitis: It is exceedingly rare and leads to cetuximab treatment discontinuation. Individualized treatment including specialist attention, similar to that provided for burn patients, is recommended.

Case Reports

First case report

43-year-old women suffering from a squamous-cell carcinoma of the hypopharynx. The patient declared alcohol abuse seven years ago, presenting alcoholic liver disease and a smoking habit of 1.5 packages per day since she was 14 years old. Computed tomographic scanning of the neck revealed a T4N0 M0 disease. Patient started treatment with neoadjuvant TPF plus cetuximab in a clinical trial (four cycles every three weeks) (Mesía et al., 2009b) Subsequently the patient initiated cetuximab combined with radiotherapy: 69.9 Gy concomitant boost accelerated radiotherapy [50.4 Gy (1.8 gy X 28 days) and 19.5 Gy (1.5 Gy X 13 days)]. Radiotherapy duration was 6.5 weeks.

After the third week of neoadjuvant TFP plus cetuximab treatment a painful edematous erythematosus rash developed in the face (Figure 1A). The patient initiated treatment with topic corticosteroids (betametasone) in the erythematosus area twice a day, combined with vaseline cream ad libitum with recovery

JCST/Vol.1 Issue 1



Figure 1: Case report 1: Evolution of the skin lesions.

1A: Painful edematous-erythematous rash in face due to TPF + cetuximab treatment.

1B: Grade 2 radiation dermatitis after two days since end of radiotherapy and cetuximab treatment.

1C: One week later: Evolution to grade 1 radiation dermatitis.

1D: Three weeks later: Evolution to nearly complete recovery.

to non-symptomatic status in only one week. Two days after the radiotherapy treatment ended, the lesion had worsened and patient developed grade 2 radiation dermatitis with patchy ulcerated and erythematosus areas (Figure 1B) and topic administration of antibiotic (mupirocin) was prescribed in combination with moisturizing cream. One week after completion of the therapy, the skin manifestations had declined to asymptomatic. The lesions improved with the treatment and healed completely (Figure 1C and 1D).

Second case report

45-year-old man suffering from a squamous-cell carcinoma of the oropharynx. The patient declared moderate alcohol abuse and a smoking habit of 1 package per day. Computed tomographic scanning of the neck revealed a T3N2bM0 irresectable disease. Patient initiated treatment with cetuximab (started dose) and one week later 69.9 Gy concomitant boost accelerated radiotherapy [50.4 Gy (1.8 gy X 28 days) and 19.5 Gy (1.5 Gy X 13 days)] was also initiated. Radiotherapy treatment lasted for 6.5 weeks. The patient that was included in a clinical trial also received adjuvant treatment with cetuximab that finalized twelve weeks later after radiotherapy (Mesía et al., 2008a) Five weeks after radiotherapy treatment was initiated patient developed severe skin toxicity on his face, with a very pruriginous diffuse edema-erythema combined with exudative follicular maculopapular lesions, conflated and forming yellow scabs (Figure 2A). Neither radiotherapy nor cetuximab treatments were discontinued and topical antibiotics (mupirocin twice a day) over the pustular areas and topical corticosteroids (betametasone twice a day) over the erythematosus areas were administered. Concomitantly, oral antihistamine treatment (one pill of ebastine) was also administered. Within one week skin was reduced, with only some maculopapular lesions and mild erythema (Figure 2B). Steroid treatment was interrupted while treatment with topical antibiotics and oral antihistamine was maintained (Figure 2C). Treatment

J Cancer Sci Ther

Volume 1(1): 028-033 (2009) - 030

Citation: Mesía R, Vilajosana E, Lozano A, Esteller L, Silvia V (2009) Management of Cutaneous Toxicity and Radiation Dermatitis in Patients with Squamous Cancer of the Head and Neck Undergoing Concurrent Treatment with Cetuximab and Radiotherapy. J Cancer Sci Ther 1: 028-033. doi:10.4172/1948-5956.1000005



Figure 2: Case report 2: Evolution of skin lesions from the 5^{th} week of concomitant treatment of cetuximab and radiotherapy.

- 2A: Lesions at 5th week of treatment.
- 2B: Lesions at 6 th week of treatment.
- 2C: Lesions at 7th week of treatment.
- 2D: Lesions five days after the end of radiotherapy treatment.



Figure 3: Case report 3: Evolution of skin lesions from one week after the end of radiotherapy plus cetuximab treatment. 3A: One week after finishing radiotherapy treatment.

- 3B: Two weeks after finishing radiotherapy treatment.
- 3C: Three weeks after finishing radiotherapy treatment.

resulted in wound healing that allowed the continuation of adjuvant treatment with cetuximab despite the prior development of skin toxicity, receiving only moisturising cream (Figure 2D).

Third case report

68 year-old man diagnosed with squamous cell cancer of the supraglottis (T4N0M0). Induction treatment in a clinical trial with TPF plus cetuximab was initiated (Mesía et al., 2009b) After two cycles and having reached complete response, only TPF treatment had to be discontinued due to the appearance of toxicity (grade 3 febrile neutropenia, grade 3 asthenia, grade 3 anorexia and grade 2 cutaneous toxicity), continuing treatment with cetuximab. Later on 6.5 week-radiotherapy concomitant treatment with cetuximab was initiated. One week after radiotherapy treatment was finalized patient developed in the neck area a suppurative

ulcer with edematous erythema that was classified as suprainfected grade 3 radiation dermatitis (Figure 3A). A sample of the drainage was obtained with a cotton swab for microbiological culture and treatment with oral antibiotic (amoxicillin clavulanic acid 500 mg/8h for a week), topical antibiotic (mupirocin cream) and topical corticosteroids on erythematous areas (betametasone) were initiated. The culture yielded multirresistant *Staphylococcus aureus*. One week after antibiotic treatment was applied a clear improvement was observed (Figure 3B). Based on the antibiogram results, oral antibiotic treatment was therefore interrupted and only topic antibiotic combined with moisturizing cream was applied. Three weeks after radiotherapy treatment was finalized a complete recovery of the skin toxicity was achieved (Figure 3C).

Fourth case report

60 year-old man diagnosed with squamous cell carcinoma of the hypopharynx. The patient declared severe alcohol abuse



Figure 4: Case report 4: Evolution of skin lesions from the 6th week of concomitant radiotherapy and cetuximab treatment

4A. 6th week of treatment with radiotherapy + Cetuximab

4B. 7th week of treatment

- 4C. 1 week after the end of radiotherapy
- 4D. 2 weeks later
- 4E. 3 weeks later
- 4F. 4 weeks later
- 4G. 5 weeks later

Volume 1(1): 028-033 (2009) - 031

Journal of Cancer Science & Therapy - Open Access

until the year before, a smoking habit of two packages per day and presented liver cirrhosis. Computed tomographic scanning of the neck revealed a T2N2bM0 disease. Patient initiated treatment with cetuximab (started dose) and one week later 69.9 Gy concomitant boost accelerated radiotherapy [50.4Gy (1.8gyX28 days) and 19.5Gy (1.5GyX13 days)] was also initiated. Radiotherapy treatment lasted for 6.5 weeks. During the sixth week of treatment patient developed grade 2 radiation dermatitis with patchy ulcerated and erythematosus areas and grade 3 mucositis that required a nasograstic tube (Figure 4A). Treatment with topic antibiotic (mupirocin) and steroids (betametasone) was initiated. Despite treatment the lesion worsened reaching grade 3 one week later (Figure 4B). Treatment with topical steroids was interrupted keeping only the topical antibiotic. One week later the lesions had worsened, with the appearance of suppurative lesions. A sample of the drainage was obtained with a cotton swab for microbiological culture, maintaining treatment with topic antibiotic (mupirocin) and adding topical corticosteroids (betametasone) for the erythematosus area. (Figure 4C). The culture yielded negative results. Treatment with moisturizing cream was initiated while antibiotic and corticosteroids treatment was discontinued. A central ulcerated area remained that led to re-initiation treatment with topical antibiotic (Figures 4D, 4E, 4F). A complete resolution of the lesions was reached after two weeks (Figure 4G).

Fifth case report

62 year-old man diagnosed with squamous cell carcinoma of the hypopharynx. The patient declared moderate alcohol and a prior smoking habit of two packages per day. Computed tomographic scanning of the neck revealed a T3N3M0 disease. Induction treatment with TPF plus cetuximab was initiated in a clinical trial (Mesía et al., 2009b), reaching local complete response and partial lymph node response. After two cycles of neo TPF the patient developed an acneiform rash in the nose area and erythematosus rash in the chin area (grade 1 skin toxicity) (Figure 5A). Treatment with topic antibiotic (mupirocin) over the acneic rash and topic corticosteroids (betametasone) over the seborrheic area was initiated and the skin toxicity was healed. Radiotherapy treatment was initiated and after four weeks grade 1 radiation dermatitis developed, with red shiny areas in the neck without lesions (Figure 5B). Treatment with moisturizing cream was initiated. After one week an edematous erythema with patchy ulcerative regions developed in the same area (grade 2 radiation dermatitis) that required administration of topical antibiotic (mupirocin) over the ulcerative regions and topic corticosteroids (betametasone) on the edematous areas combined with the moisturizing cream (Figure 5C). At the sixth week of radiotherapy the patient developed grade 3 radiation dermatitis with exudative edematous erythema, that was treated with moisturizing cream and topic antibiotics. At the seventh week of radiotherapy suppurative ulcerative lesions developed that required culture of the drainage and administration of oral antibiotic (amoxicillin and clavulanic acid 500mg/8h) combined with topical antibiotic over the ulcerative lesions (Figure 5D). During the first week post-radiation treatment grade 3 radio dermatitis persisted and the culture yielded negative results (Figure 5E). Topical antibiotic was continued and the 10-day oral antibiotic treatment was completed. During the next two weeks treatment with collagenase ointment (Iruxol mono) was applied that led to wound healing in

JCST/Vol.1 Issue 1



Figure 5: Case report 5: Evolution of skin lesions that appeared after two cycles of neo TPF.

5A: After two cycles of neo TPF: development of grade 1 skin toxicity 5B: 4th week after radiotherapy treatment: development of grade 1 radiation dermatitis

5C: 5th week of radiotherapy: worsening of the symptoms (grade 2 skin toxicity). A topical treatment was initiated.

5D: 7^{th} week of radiotherapy: an oral antibiotic treatment was administered

5E: 1st week after radiotherapy: worsening of the lesions

5F: 2^{nd} week after radiotherapy: initiation of treatment with collagenase ointment

5G: 3rd week after radiotherapy: improvement of the lesions while receiving collagenase treatment

5H: 4th week after radiotherapy dermatitis: complete resolution of the lesions.

the fourth week after radiation treatment (Figures 5F and 5G).

Conclusions

In summary, cutaneous toxicity and radiation dermatitis in patients with SCCHN undergoing concurrent treatment with cetuximab and radiotherapy are relative easily manageable and only in very rare instances lead to treatment discontinuation. It must be emphasized the need of fulfilling general hygiene measurements as well as early establishment of topical treatment once the lesions appear to prevent any potential lesion worsening. It should also prioritize the use of topical versus oral treatments on this p.o. heavily treated population. Lesion **Citation:** Mesía R, Vilajosana E, Lozano A, Esteller L, Silvia V (2009) Management of Cutaneous Toxicity and Radiation Dermatitis in Patients with Squamous Cancer of the Head and Neck Undergoing Concurrent Treatment with Cetuximab and Radiotherapy. J Cancer Sci Ther 1: 028-033. doi:10.4172/1948-5956.1000005

monitoring should include weekly visits for minor/moderate lesions and twice per week visits for severe cases.

References

- Adelstein DJ, Li Y, Adams GL, Wagner H Jr, Kish JA, et al. (2003) An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. J Clin Oncol 21: 92-98. » CrossRef » PubMed » Google Scholar
- Bernier J, Bonner J, Vermorken JB, Bensadoun RJ, Dummer R, et al. (2008) 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. » CrossRef » PubMed » Google Scholar
- Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, et al. (2006) Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med 354: 567-578. » CrossRef » PubMed » Google Scholar
- 4. Bourhis J, Lapeyre M, Tortochaux J, Rives M, Aghili M, et al. (2006) Phase III randomized trial of very accelerated radiation therapy compared with conventional radiation therapy in squamous cell head and neck cancer. A GORTEC trial. J Clin Oncol 24: 2873-2878. » CrossRef » PubMed » Google Scholar
- Brizel DM, Albers ME, Fisher SR, Scher RL, Richtsmeier WJ, et al. (1998) Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck. N Engl J Med 338: 1798-1804. » CrossRef » PubMed » Google Scholar
- Burtness B (2005) Cetuximab and cisplatin for chemotherapyrefractory squamous cell cancer of the head and neck. J Clin Oncol 23: 5440-5442. » CrossRef » PubMed » Google Scholar
- 7. Calais G, Alfonsi M, Bardet E, Sire C, Germain T, et al. (1999) Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. J Natl Cancer Inst 91: 2081-2086. » CrossRef » PubMed » Google Scholar
- Hitt R, Irigoyen A, Nuñez J, Grau J, Saenz JG, et al. (2007) Phase II study of combination cetuximab and weekly paclitaxel in patients with metastatic/recurrent squamous cell carcinoma of head and neck (SCCHN): Spanish Head and Neck Cancer Group (TTCC). J Clin Oncol 25. » CrossRef » Google Scholar
- Huguenin P, Beer KT, Allal A, Rufibach K, Friedli C, et al. (2004) Concomitant cisplatin significantly improves locoregional control in advanced head and neck cancers treated with hyperfractionated radiotherapy. J Clin Oncol 23: 4665-4673. » CrossRef » PubMed » Google Scholar
- 10. Jeremic B, Shibamoto Y, Milicic B, Nikolic N, Dagovic A, et al. (2000)

Hyperfractionated radiation therapy with or without concurrent low dose daily cisplatin in locally advanced squamous cell carcinoma of the headk and neck: a prospective randomized trial. J Clin Oncol 18: 1458-1464. » CrossRef » PubMed » Google Scholar

- 11. Langer CJ, Lee LW, Patel UA, Shin DM, Argiris AE, et al. (2008) 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 26. » CrossRef » Google Scholar
- 12. Mesia R, Rueda A, Vera R, Lozano A, Medina J, et al. (2008) Safety report of a randomized phase II trial to evaluate the combination of cetuximab plus accelerated concomitant boost radiotherapy (RT) followed or not followed by cetuximab monotherapy in patients (pts) with locally advanced squamous cell carcinoma of the oropharynx. J Clin Oncol 26.
- 13. Mesia R, Vázquez S, Grau JJ, García-Sáenz JA, Bayona C, et al. (2009) A single arm phase II trial to evaluate the combination of cetuximab plus taxotere (T), cisplatin (P) and 5-fluorouracil (F) (TPF) as induction chemotherapy (IC) in patients (pts) with unresectable SCCHN. J Clin Oncol 27.
- Parkin DM, Bray F, Ferlay J, Pisani P (2005) Global cancer statistics, 2002. CA Cancer J Clin 55: 74-108. » CrossRef » PubMed » Google Scholar
- 15. Pfister DG, Su YB, Kraus DH, Wolden SL, Lis E, et al. (2006) 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. » CrossRef » PubMed » Google Scholar
- 16. Schantz SP, Harison LB, Forastiere AA (1997) Tumors of the nasal cavity and paranasal sinuses, nasopharynx, oral cavity, and oropharynx. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds.: Cancer: Principles and Practice of Oncology, Philadelphia. Pa: Lippincott-Raven Publishers 2206: 797-860.
- 17. Vermorken JB, Bourhis J, Trigo J, Kies M, Leon X, et al. (2005) Cetuximab in recurrent/metastatic (R&M) squamous cell carcinoma of the head and neck (SCCHN) refractory to first-line platinum-based therapies. J Clin Oncol 23. » CrossRef » Google Scholar
- Vermorken JB, Mesia R, Rivera F, Remenar E, Kawecki A, et al. (2008) Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med 359: 1116-1127. » CrossRef » PubMed » Google Scholar
- Wendt TG, Grabenbauer GG, Rödel CM, Thiel HJ, Aydin H, et al. (1998) Simultaneous radiochemotherapy versus radiotherapy alone in advanced head and neck cancer: a randomized multicenter study. J Clin Oncol 16: 1318-1324. » CrossRef » PubMed » Google Scholar
- 20. International Agency for Research on Cancer: CANCERMondial. www-dep.iarc.fr