

Cetuximab and Oral Mucositis: Is it Different from Oral Mucositis Caused by Other Drugs?

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Abstract

Purpose: To estimate frequency of oral mucositis in treatment for head and neck cancer with radiotherapy and concurrent cetuximab and to determine whether it has different characteristics from mucositis caused by other drugs.

Materials and methods: Subjects with locally advanced, primary non-metastatic, squamous cell carcinoma located in the oropharynx were treated with radiation therapy plus concomitant cetuximab.

Results: None of patients received their full planned course of combination treatment due to excessive mucosal toxicity. All patients developed oral mucositis within about 10-15 days: it began directly, without escalation, as grade ≥ 3 ; it was associated with severe pain and trismus; it was never associated to specific supra-infections; the evolution and the consequent resolution of clinical discomfort required several days and the treatment with corticosteroids did not represent the solution formula.

Conclusion: Cetuximab induced oral mucositis have the following specific characteristics: time of onset, mode of clinical expression, severity, association with trismus and minimal response to corticosteroid therapy. Considering that the majority of studies do not reveal oral toxicity associated with cetuximab, future clinical trials should focus on specific topics to improve the definition of documented oral toxic effects.

Keywords: Cetuximab; Chemotherapy; Oral mucositis; Drugs

Introduction

Oral mucositis represents a common complication of non-surgical treatment for head and neck cancer. It is associated with pain, dysgeusia and dysphagia, compromising nutritional status: therefore oral mucositis has a significant impact on patient's quality of life. Its appearance depends on radiation and/or cytotoxic regimen adopted and on subjective-related factors, such as age, patient's diagnosis and pre-treatment oral condition [1]. Oral side effects can induce a radiation total dose reduction or a treatment schedule modification; severe oral mucositis, consequently, can determine a discontinued treatment, to allow resolution of toxicity [2]. The evaluation of oral mucositis is paramount to compare different treatment efficacy, in term of survival too, because treatment disruptions can impact on local disease control. We analysed data on our head and neck database to estimate frequency and graveness of oral mucositis in patients treated with radiotherapy and concurrent cetuximab and to determine whether it has different characteristics from mucositis caused by other drugs.

Patients and Methods

Subjects with locally advanced, primary non-metastatic, squamous cell carcinoma located in the oropharynx were included. Patients received a complete work-up including count blood cells and determination of serum electrolyte levels, nasopharyngolaryngoscopy with biopsy, CT and/or RM of the head and neck, chest CT and preventive dental care.

Cetuximab was administered once a week. Patients received the initial induction dose of 400 mg/m² one week before radiation therapy, followed by 250 mg/m²/week until the end of the radiation therapy period. A prophylactic premedication with corticosteroids and antihistamines was performed to reduce infusion-related reactions. According to recommendation by the manufacturer cetuximab therapy was interrupted if severe reaction (\geq grade 3) occurred [3].

Two radiation schedules were used: conventional radiotherapy (70 Gy in 35 daily fractions, 5 days/week, over 7 weeks) and simultaneous integrated boost (68-52.7 Gy in 31 daily fractions, 5 days/week, over 6 weeks).

Toxicity was classified by type and grade according to NCI-CTC version 4.0 [4]. Clinical photographs were taken of grade ≥ 3 mucosal reactions.

Results

Patients' characteristics

Between May 2011 and September 2012, 5 consecutive patients with locally advanced squamous cell carcinoma of the oropharynx were treated with radiation therapy plus concomitant cetuximab at our Department. Demographic and clinical characteristics of patients are listed in Table 1. All patients were males, with PS 0-1 and average age of 63.2 years (range 54-69). All tumours were classified as stage IVA because of pathological regional lymph nodes.

Treatment compliance

All patients completed the cetuximab induction phase and all

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Characteristics	n	%
Sex		
Male	5	100
Female	0	
Age		
average	63.2	
range	54-69	
Performance status		
0	3	60
1	2	40
Histology		
Squamous cell carcinoma	5	100
T-stage		
1-2	3	60
3-4	2	40
N-stage		
2b	3	60
2c	2	40
AJCC stage		
IVA	5	100
Treatment		
RT + cetuximab	5	100

Table 1: Demographic and tumour characteristics of patients.

Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Mucositis oral (clinical exam)	Erythema of the mucosa	Patchy ulcerations or pseudo membranes	Confluent ulcerations or pseudo membranes; bleeding with minor trauma	Tissue necrosis; significant spontaneous bleeding	Death
Mucositis oral (functional/symptomatic)	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death

Table 2: Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

patients began the concomitant treatment. None of patients received their full planned course of combination treatment due to excessive mucosal toxicity. Target therapy was definitively suspended in all patients: 1 patient tolerated only 2 cycles of cetuximab; 2 patients received 3 cycles and 2 patients 4 cycles of cetuximab. Radiation therapy was interrupted for 12 days (range 10-17) in 4 patients; only 1 patient received radiation total dose as current practice.

Acute toxicity

Toxicities reported included oral mucositis, dysphagia, pain and skin reactions.

All patients developed oral mucositis within about 10-15 days: it began directly, without escalation, as grade 3 in 4 patients and as grade 4 in 1 patient. This symptom was associated with severe pain and trismus in all cases.

Radiation-induced skin toxicity was recorded: it occurred as G4 in 2 patients and G3 in the other patients.

Symptomatic and altered eating/swallowing (G2) was recorded in 4 patients, while 1 patient presented a severe dysphagia (G3).

Discussion

Oral mucositis monitoring is a crucial point in the assessment of therapies. The introduction of target therapy generated several adverse events which are not well characterized by the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0 and its previous versions (NCI-CTCAE version 1.0, 2.0 and 3.0) [5]. However this toxicity criteria instrument is the select scoring

system used by the majority of investigators to document toxic effects of treatment schedule. This discordance represents interference in the optimal utilization of new therapies and in the evaluation of new drug real benefit and efficacy compared to currently available therapy.

Nowadays radiochemotherapy represents an alternative approach to surgery, in concept of organ preservation, for patients with locally advanced squamous cell carcinomas of the head and neck.

Cisplatin-based chemotherapy and radiotherapy is considered the standard regimen [6], although cisplatin's acute toxicity can be so severe that most of patients received only two of the recommended three cycles of treatment [7]. To optimize treatment tolerability, a targeted therapy approach was proposed, considering the over expression of Epidermal Growth Factor Receptors (EGFR) in head and neck cancers. The benefit of cetuximab was comparable to advantage reported in cisplatin-based therapy, but considering that a definitive randomized trial comparing radiation therapy plus cisplatin versus radiation therapy plus cetuximab is lacking, it remains only a good indirect comparison [7].

While radiation dermatitis in patients receiving cetuximab concomitantly with radiotherapy is recognized as a common side effects [8-13], oral mucositis is underestimate [9,12-14]. Mucositis is an important consequence of cytotoxic or biologic agents with concurrent radiation in head and neck cancer, and the severity of mucositis may even be higher in EGFR inhibitor therapy compared with cisplatin regimen [13]. The NCI-CTCAE severity grading scale seems to be not so appropriate to measure oral mucositis, because it is based on patient's ability to eat and drink combined with objective signs of mucositis, but in separate scales (Table 2) [4,14,15]. The severity of pain and the inability to eat correctly were difficult to capture properly

from the scale-system and all these unmeasured factors could produce significant bias [16].

Cetuximab oral mucositis presents with general erythema, less ulcerative but more widespread than classical ulcerative mucositis recorded with radiation and cytotoxic agents, such as cisplatin; it is associated with pain, trismus and complete inability to tolerate solids and fluids [16,17]. In our series, further features have emerged: oral mucositis appeared unexpectedly as a severe grade toxicity within about 10-15 days the start of concomitant therapy and it was never associated to specific supra-infections; the evolution and the consequent resolution of clinical discomfort required several days and the treatment with corticosteroids did not represent the solution formula, it was not as effective as in other types of mucositis by other drugs [17-21].

Our study is limited because of the small patients group, but the specific focus of this study was to demonstrate the impact of cetuximab plus radiotherapy on oral mucositis evaluation and not to assess the relation between therapy and response, as various authors have done [9,12-14,18,22]. As such, we chose not to include a correlation between concomitant treatment and control parameters of response.

Limited data exist regarding whether cetuximab increases the rate of oral mucositis in patients with head and neck cancer. Most of the little information derived from randomized-controlled trials that were not designed to compare the mucositis rates among different treatment modalities.

The Bonner's study [14] claimed concomitant radiotherapy plus cetuximab regimen not exacerbated the common mucositis associated with radiotherapy: mucositis \geq G3 was recorded in 56% of patients. Lord et al. [9] described only a case of mucositis \geq G3 in their series of 14 patients. Whereas our data indicate that cetuximab, in combination with local radiation therapy of the head and neck area, emphasized undesirable effects typical of radiation therapy, such as mucositis, radiation dermatitis and dysphagia. Data from day-by-day medical practices reflected the true information: the addition of cetuximab improved the risk of mucositis and all patients developed oral mucositis \geq G3 (Figure 1). An increased risk of oral mucositis also was demonstrated in other trials that used cetuximab in association with radiation therapy. Pryor et al. [12] reported mucositis \geq G3 in 10 of 13 patients. Walsh et al. [13] identified oral mucositis \geq G3 in 25 (74%)

of their 34 patients. Ang et al. [23] (RTOG trial 0522) also showed an increase of oral mucositis G3/G4 adding Cetuximab to Cisplatin (43% versus 33%).

Therefore an accurate grading of oral adverse events due to EGFR inhibitor is paramount for a correct management strategy, because mucositis can complicate nutritional status, limiting patient's intake of solids and liquids and can compromise the delivery of scheduled radiation doses. Despite in literature cetuximab figures as a drug with an acceptable tolerability profile [17], oral mucositis, as added toxic effect, must be considered in future head and neck cancer trials and in patients care, because it has a significant impact on regularly treatment and on patient's quality of life.

Conclusion

There is a paucity of evidence-based data on the evaluation of oral mucositis in the cetuximab-based treatment of locally advanced head and neck squamous cancers. In our experience, Cetuximab induced oral mucositis have the following specific characteristics: time of onset, mode of clinical expression, severity, association with trismus and minimal response to corticosteroid therapy. Studying these peculiarities, we could arrive at the formulation of the physiopathology of Cetuximab induced mucositis and develop most appropriate therapeutic supports.

Considering that the majority of studies do not reveal oral toxicity associated with cetuximab, future clinical trials should focus on specific topics to improve the definition of documented oral toxic effects.

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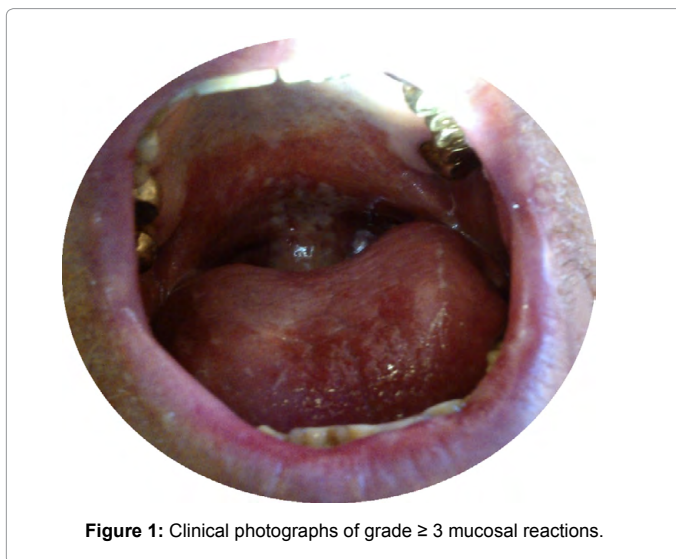


Figure 1: Clinical photographs of grade \geq 3 mucosal reactions.

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