Original article

Incidence of mucositis in patients with head and neck squamous cell carcinoma treated with radiotherapy plus cetuximab: a pilot study

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Abstract – Objectives: Cetuximab-induced mucositis has been poorly reported in the literature. The aim of this pilot study was to determine the severity and incidence of oral mucositis in patients treated with radiotherapy plus cetuximab.

Materials and methods: Patients treated for a head and neck squamous cell carcinoma (HNSCC) by radiotherapy plus cetuximab (C+) were included. The incidence and severity of mucositis, dysphagia and use of analgesic drugs were reported.

Results: 25 patients treated with radiotherapy plus cetuximab were included. The absolute risk of developing severe mucositis was 0.40. Treatment interruption was necessary in 16% of patients, and hospitalization due to side effects was necessary in 12% of patients.

Conclusions: Despite the small number of patients, incidence of severe mucositis seems to be higher in patients treated with radiotherapy plus cetuximab. An increased use of morphine appears to be correlated with the severity of mucositis. Pain resulting from oral mucositis is predictive of oral functional impairment. This pilot study highlights the lack of knowledge on cetuximab-induced mucositis, in association with radiotherapy. A prospective multicenter study should be conducted to more precisely evaluate the incidence and severity of mucositis, the time of occurrence, and the impact on quality of life and treatment interruption of patients.

Résumé – Incidence des mucites chez les patients présentant un carcinome des voies aéro-digestives supérieures traités par radiothérapie et cetuximab : étude pilote. Objectifs : La littérature apporte peu de données sur la mucite induite par le cétuximab. Le but de cette étude préliminaire est de déterminer l’incidence et la sévérité des mucites chez les patients traités par radiothérapie plus cétuximab.

Matériel et méthode : Les patients traités par radiothérapie plus cetuximab pour un cancer des voies aéro-digestives supérieures ont été inclus dans cette étude. L’incidence et la sévérité des mucites, la dysphagie et la nécessité de recours à des antalgiques ont été observées.

Résultats : 25 patients ont été inclus. Le risque absolu de développer une mucite sévère était de 0,40. Une interruption thérapeutique a été nécessaire pour 16 % des patients, et 12 % des patients ont du être hospitalisés à cause des effets indésirables du traitement.

Discussion : Malgré le faible nombre de patients inclus, l’incidence de la mucite sévère semble plus important chez les patients traités par radiothérapie plus cétuximab. L’utilisation majorée des morphiniques est en corrélation avec la sévérité de la mucite. La douleur induite par la mucite est prédictive des altérations des fonctions orales. Cette

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Mots clés : cancer des voies aéro-digestives supérieures / toxicité / mucite orale / cetuximab mucositis
The combined use of external radiotherapy and cetuximab, a monoclonal antibody, is an option for the treatment of locally advanced head and neck squamous cell carcinoma (HNSCC) [1, 2]. Indeed, a phase-III clinical trial showed a 32% decrease of local tumor progression and a 26% decrease in mortality in patients treated with radiotherapy and cetuximab vs. radiotherapy alone [3]. Although the cutaneous side effects of cetuximab have been well studied, the incidence and severity of oral mucositis, a well-established side effect of radiotherapy, remain unclear [4]. Some authors report an increase in the incidence and severity of mucositis in patients treated with cetuximab [5] whereas others show no difference between patients treated with radiotherapy alone or with radiotherapy plus cetuximab [2].

Therefore, the aim of this pilot study was to evaluate the severity and incidence of oral mucositis in patients treated with radiotherapy plus cetuximab. An additional objective was to report the type of analgesic drugs required, and the occurrence and treatment of oral and pharyngeal events. Finally, the last goal of the study was to determine which critical elements should be collected for a better understanding and management of this specific side effect.

Patients and methods

The study population was retrospectively recruited between January 2009 and January 2011, and prospectively followed up for at least 12 months. Twenty-five consecutive patients matching the inclusion criteria were included. The inclusion criteria were as follows: patients presenting with HNSCC and treated with known doses of radiotherapy plus cetuximab, and who had benefit of weekly oral assessment. The exclusion criteria were as follows: patients treated for another type of tumor, or with unknown doses of radiotherapy and/or cetuximab.

The following data were prospectively collected and stored in a database: age, gender, weight, cigarette smoking, alcohol consumption, date of start and end of treatment, tumor stage, comorbidities, use of neoadjuvant chemotherapy, dose and modality of radiotherapy, and dose of cetuximab planned and administered. These side effects were particularly examined: incidence and severity of mucositis, dysphagia and erythema. Moreover, the need to treat the side effects with analgesics or topical agents or even to interrupt the treatment or be hospitalized because of the side effects was also noted. The level of analgesia required was determined according to the WHO classification. The incidence of mucositis was recorded and the severity was graded according to the WHO scale. Finally, the absolute risk of developing severe mucositis in patients treated by radiotherapy plus cetuximab was determined.

Results

25 patients were included in the study, of which 20 were men and five were women. All patients completed treatment and reached the minimum follow-up period of 12 months after the end of treatment.

The characteristics of the patients are presented in Table I. Initial tumor locations were: oral cavity (n = 6), hypopharynx (n = 5), oropharynx (n = 8), larynx (n = 4), nasopharynx (n = 1), and node (n = 1). 40% of were treated with intensity-modulated radiation therapy (IMRT); the protocol for IMRT was 2.2 Gy per fraction with a simultaneous integrated boost. The mean dose of cetuximab administered was 3201.64 mg (1550–4800), 682.63 mg (310–800) were administrated at the first course; 7 to 8 courses were planned, and 3 to 8 courses realized.

Table I. Characteristics of the study population.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Age (years)</td>
<td>62.04 (35–78)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>65.92 (50–97)</td>
</tr>
<tr>
<td>Cigarette smoking (pack/year)</td>
<td>43.33</td>
</tr>
<tr>
<td>Comorbidities (n)</td>
<td>10</td>
</tr>
<tr>
<td>Lymph node surgery (n)</td>
<td>9</td>
</tr>
<tr>
<td>Neoadjuvant chemotherapy (n)</td>
<td>14</td>
</tr>
<tr>
<td>IMRT (n)</td>
<td>10</td>
</tr>
<tr>
<td>Dose of radiation (Gy)</td>
<td>66.04 (45–70)</td>
</tr>
<tr>
<td>Dysphagia (n)</td>
<td>21</td>
</tr>
<tr>
<td>Mucositis (n)</td>
<td>25</td>
</tr>
<tr>
<td>Cutaneous erythema (n)</td>
<td>25</td>
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</tbody>
</table>

Side effects were highly prevalent: dysphagia was reported in 84% of patients, and mucositis in all patients, cutaneous erythema in 100% of patients. Of the 21 patients presenting with dysphagia, 6 were grade I (WHO scale), 3 grade II, 2 grade III and 10 an unknown grade. Of these patients, two had a gastrostomy and six enteral nutrition. All patients without oral nutrition received full-course cetuximab. Weight loss between treatment start and end was 13.6 kg (1 to 21) in group C+, which corresponds to a weight loss of 17.4%.
Pretreatment oral examination was normal in all patients, without inflammation. All patients had a personal oral care plan. Grade 1 or 2 mucositis was reported in 60% of patients, whereas severe mucositis was reported in 40% of patients (Table II). The absolute risk of developing severe mucositis was 0.40. The use of morphine concerned 11 patients. 16% of patients had to stop treatment (cetuximab courses for all patients, and radiotherapy for 2 patients with a minimal dose of 56 Gy), and 12% of patients were hospitalized because of the side effects (i.e., dysphagia or mucositis) (Table III). Oral candidosis was also reported and treated with antifungal agents, sodium bicarbonate and/or topical agents like xylcaïne. 75% of patients had a cutaneous rash or folliculitis.

Table II. Incidence of oral mucositis.

<table>
<thead>
<tr>
<th>Grade of mucositis</th>
<th>(n = 25)</th>
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<tbody>
<tr>
<td>Grade 1</td>
<td>6</td>
</tr>
<tr>
<td>Grade 2</td>
<td>9</td>
</tr>
<tr>
<td>Grade 3</td>
<td>10</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
</tr>
</tbody>
</table>

Table III. Use of analgesics to treat oral mucositis.

<table>
<thead>
<tr>
<th>Level of analgesia</th>
<th>(n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>3</td>
</tr>
<tr>
<td>III</td>
<td>11</td>
</tr>
</tbody>
</table>

These results seemed to indicate that severe mucositis was more frequent in patients treated with radiotherapy plus cetuximab. However, the small number of patients did not allow reaching statistical significance.

Discussion

In the literature, few studies have reported the incidence of cetuximab-induced mucositis and oral side effects. In Bonner et al.’s trial [2], few details were given about mucositis, as it was not the main objective of the study. In addition, patients with grade 3 or more had a very high incidence, especially for radiotherapy alone, and one may wonder if this group did not include grade 2 mucositis or about the scale used for scoring mucositis. Pryor et al. examined the incidence and severity of mucositis in 13 patients and compared it with previously reported results [2, 3]. They noted that 77% of patients had mucositis, and treatment interruption was necessary in 31% of those patients. Bonner et al. reported an incidence of grade 3 to 4 mucositis, similar to those patients treated with radiotherapy alone [2]. Lord et al. found a higher incidence of grade 3 to 4 toxicity [6]. They reported severe toxicity in 36% of patients, including grade 4 mucositis in one patient among a total of 14. Thus, only 50% of patients completed the full course of cetuximab treatment. Walsh et al. confirmed the results of the pilot study and of Pryor et al. [7].

More recently, a review of the literature regarding the side effects of targeted therapies deplored the lack of complete oral examination to assess the incidence and severity of cetuximab-induced mucositis [8]. This pooled analysis synthesized 24 studies on the side effects of epidermal growth factor receptor inhibitors (EGFRi). Only 6 studies focused on cetuximab for the treatment of HNSCC. The incidence of severe mucositis in these studies was 56% [2], 26% [9], 34% [10], 85% [11], 29% [12] and 69% [13]. However, because of the great heterogeneity between populations, one cannot draw any firm conclusion from this review on the incidence of cetuximab-induced mucositis. Moreover, nearly half of the patients included in the review came from the study by Bonner et al. [2]. Nonetheless, the authors observed a higher incidence of mucositis in patients treated with adjuvant cetuximab and concluded to a relative risk for developing severe mucositis of 1.8.

Alongi et al. reported 9% of grade 1, 36% of grade 2 and 45% of grade 3 mucositis in a series of 22 elderly and chemotherapy-ineligible patients treated with radiotherapy plus cetuximab [14]. The results obtained in our pilot study are similar, as 60% of patients had grade 1 to 2 mucositis, and 40% of patients had grade 3 to 4 mucositis. Mucositis occurred during the third or fourth week of treatment with 800 to 1600 mg of cetuximab and a radiation dose of 25 to 40 Gy. Considering patients treated with radiotherapy alone, Trotti et al. observed a rate of 34% of severe mucositis with conventional radiotherapy [15]. In the study by De Arruda et al., 38% of patients treated with IMRT had grade 3 mucositis, and 8% and 54% of patients had grade 1 and 2 mucositis, respectively [4]. In most studies, the scale used to grade mucositis is not detailed, and is thus open to various interpretations of the different grades.

Dysphagia (21 out of 25 patients) mainly affected patients with grade 2 and 3 mucositis and seemed to be highly associated with mucositis. One may also deplore the lack of data regarding the dose of cetuximab responsible for an increase in the occurrence of mucositis or dysphagia. No data on weight loss was available for 12 patients. However, the weight loss has a major impact on prognosis, especially when the weight rapidly decreases (i.e., –17.4% in 3 months). It seems that when the patient had a combination of treatments, such as chemotherapy plus radiotherapy or radiotherapy plus cetuximab, weight loss was more significant. However, the low number of data available did not allow drawing statistical conclusions. One may consider that a more important weight loss is associated with a poorer prognosis and that this element should also be considered when establishing a therapeutic strategy.

The treatment of oral mucositis is not well established. Recently, the Multinational Association for Supportive Care in Cancer (MASCC) Skin Toxicity Study Group proposed clinical...
practice guidelines for the prevention and treatment of EGFRi-associated toxicity, including skin and oral mucosa [16]. Mucositis is a rare side effect in patients treated with cetuximab alone and occurs most often when cetuximab is co-administered with radiotherapy in the treatment of HNSCC. All the prevention and treatment strategies proposed recommend a previous assessment of oral health and the development of an individual plan of care to restore and/or maintain optimal oral hygiene. Treatments with level 1 evidence (i.e., from high-powered randomized controlled trials) include palifermin and cryotherapy, which have never been used in EGFRi studies, and also chlorhexidine, low-level laser therapy, coating agents, steroids and growth factors. Systemic administration of pentoxifylline has been evaluated in patients treated with cetuximab and seems to be recommended by a consensus of experts. In this pilot study, conventional treatments have been used, such as oral hygiene, personal oral care plan, mouth rinses with bicarbonate and regular follow-up assessment.

An increased use of morphine seems to be correlated with the severity of mucositis. It highlights the incidence and importance of the high cost of these side effects, in terms of money, time, quality of life and prognosis [17]. Moreover, pain resulting from oral mucositis is highly predictive of oral functional impairment. On the other hand, one may wonder if there is a correlation between the severity of skin rash and oral mucositis. This should be investigated in a further study [18].

This pilot study highlights the lack of knowledge on the incidence and severity of cetuximab-induced mucositis in association with radiotherapy. In the study by Bonner et al. [2], this adverse effect is probably underestimated. An eventual higher rate of mucositis induced by cetuximab is a major factor impacting the quality of life and prognosis of patients, which should thus be taken into account when establishing a therapeutic strategy, especially between radiotherapy + chemotherapy and radiotherapy + cetuximab. A prospective multicenter study should be conducted to more precisely evaluate the incidence and severity of mucositis, time of occurrence, and impact on the quality of life and treatment interruption of patients. Data including mucositis, oral health and dysphagia should be collected weekly for a better evaluation of the chronology of adverse events.

Competing interests: none

References


