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Original article

Toxicity and efficacy of cetuximab associated with several modalities of IMRT for locally advanced head and neck cancer



Toxicité et efficacité du cétuximab associé à différentes modalités de radiothérapie conformationnelle avec modulation d'intensité pour les carcinomes évolués de la tête et du cou

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ABSTRACT

Purpose. – Intensity-modulated radiation therapy (IMRT) has shown its interest for head and neck cancer treatment. In parallel, cetuximab has demonstrated its superiority against exclusive radiotherapy. The objective of this study was to assess the acute toxicity, local control and overall survival of cetuximab associated with different IMRT modalities compared to platinum-based chemotherapy and IMRT in the ARTORL study (NCT02024035).

Patients and method. – This prospective, multicenter study included patients with epidermoid or undifferentiated nasopharyngeal carcinoma, epidermoid carcinoma of oropharynx and oral cavity (T1–T4, M0, N0–N3). Acute toxicity, local control and overall survival were compared between groups (patients receiving cetuximab or not). Propensity score analysis at the ratio 1:1 was undertaken in an effort to adjust for potential bias between groups due to non-randomization.

Results. – From the 180 patients included in the ARTORL study, 29 patients receiving cetuximab and 29 patients treated without cetuximab were matched for the analysis. Ten patients (34.5%) reported acute dermal toxicity of grade 3 in the cetuximab group versus three (10.3%) in the non-cetuximab

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group obtained after matching ($P=0.0275$). Cetuximab was not significantly associated with more grade 3 mucositis ($P=0.2563$). There were no significant differences in cutaneous or oral toxicity for patients treated with cetuximab between the different IMRT modalities ($P=1.000$ and $P=0.5731$, respectively). There was no significant difference in local relapse-free survival ($P=0.0920$) or overall survival ($P=0.4575$) between patients treated with or without cetuximab.

Conclusion. – Patients treated with cetuximab had more cutaneous toxicities, but oral toxicity was similar between groups. The different IMRT modalities did not induce different toxicity profiles.

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R É S U M É

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Objectif de l'étude. – L'intérêt de la radiothérapie conformationnelle avec modulation d'intensité (RCMI) a été montré pour le traitement des carcinomes de la tête et du cou. L'association avec le cétuximab a par ailleurs démontré sa supériorité sur une radiothérapie exclusive. L'objectif de cette étude était d'évaluer la toxicité aiguë, le contrôle local et la survie globale chez des patients traités par différentes modalités de RCMI (tomothérapie, arcthérapie volumétrique modulée) et recevant du Cetuximab comparé à des sels de platine inclus dans l'essai ARTORL (NCT02024035).

Patients et méthode. – Cet essai prospectif multicentrique a inclus des patients atteints de carcinome épidermoïde ou indifférencié du nasopharynx, de l'oropharynx et de la cavité orale (de stades T1–T4, M0, N0–N3). La toxicité aiguë, le contrôle local et la survie globale ont été comparés entre les groupes (RCMI avec ou sans cétuximab). Un score de propension 1:1 a été créé afin d'ajuster les groupes et de compenser d'éventuels biais liés à l'absence de randomisation.

Résultats. – Des 180 patients inclus dans l'étude ARTORL, 29 patients ont reçu du cétuximab et été appariés à 29 patients traités sans cétuximab. Dix patients (34,5 %) du groupe recevant du cétuximab ont souffert d'une toxicité cutanée de grade supérieur ou égal à 3 contre trois dans le groupe sans cétuximab ($p=0,0275$). Aucune différence de toxicité muqueuse supérieure ou égale à 3 ($p=0,2563$) n'a été mise en évidence. Les différentes modalités de RCMI n'ont pas engendré de différences de toxicité cutanée ($p=1,000$) ou muqueuses ($p=0,5731$). Aucune différence significative de taux de contrôle local ($p=0,0920$) ou de survie globale ($p=0,4575$) n'a été retrouvée entre les groupes.

Conclusion. – Les patients du groupe avec cétuximab ont souffert d'une toxicité cutanée plus importante, mais aucune différence de toxicité muqueuse n'a été retrouvée. Les différentes modalités de RCMI n'ont pas influencé la toxicité.

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1. Introduction

Intensity-modulated radiation therapy (IMRT) has shown its interest for preservation of salivary gland function in upper aerodigestive tract, without compromising locoregional control and survival, making it a new standard of care for head and neck radiotherapy [1–3]. In parallel, targeted biotherapy have developed in the field, and the Bonner trial showed that treatment of locoregionally advanced head and neck cancer with concomitant high-dose radiotherapy plus cetuximab improved locoregional control compared to radiotherapy alone [4,5]. Results of the TREMPIN and RTOG 0522 studies showed that cetuximab had equivalent or worse efficacy when compared with chemoradiotherapy [6,7]. The toxicity of cetuximab, when used with radiotherapy, should not be overlooked, since it was also reported that this association enhanced cutaneous and oral toxicities, resulting in low treatment compliance and delays in completing radiotherapy [8]. Guidelines have been published to better manage this toxicity [9]. All these studies have been mostly performed with 3D conformational radiotherapy.

Retrospective and prospective studies have been published to report the specific toxicity of the association of IMRT and epidermal growth factor receptor (EGFR) inhibitors [10–12]. It could however be argued that the increased total dose and increased volume irradiated could modify the cutaneous or oral toxicity. Moreover, several IMRT modes are available, and these different modes have dosimetric consequences, which could result in different doses to the surrounding organs at risk [13,14]. The objective was to compare toxicity in patients treated with concomitant chemotherapy

or cetuximab across several IMRT modalities (Tomotherapy®, Varian RapidArc® or Elekta Volumetric-modulated Arc Therapy®). This ancillary study was performed on the patients included in the ARTORL study (NCT02024035) and was approved by the ARTORL steering committee.

2. Methods

2.1. Patients

This prospective, multicenter study included patients at least 18 years of age, with epidermoid or undifferentiated nasopharyngeal (UCNT) carcinoma, epidermoid carcinoma of oropharynx and oral cavity (T1–T4, M0, N0–N3), a WHO performance status 2 or below, treated by exclusive radiotherapy of bilateral cervical lymph nodes. Exclusion criteria were metastatic diseases, previous invasive cancer, unilateral cervicofacial radiotherapy under consideration, postoperative radiation therapy, treatment with amifostine, brachytherapy, and indications for re-irradiation. Fourteen French centers participated. All patients provided written informed consent. The study was conducted in accordance with the ethical principles for medical research involving human subjects developed in the Declaration of Helsinki by the World Medical Association (WMA). The study received approval in France from the National ethics committee (No. 909226) and the National committee for protection of personal data (No. 09-203).

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