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Original article

Radiotherapy combined with cetuximab for locally advanced head and neck cancer: Results and toxicity

Association radiothérapie–cétuximab chez des patients atteints d'un carcinome épidermoïde ORL localement évolué non opérable : résultats et effets secondaires

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ABSTRACT

Purpose. – To describe the clinical results and tolerance of the combined treatment with radiotherapy and cetuximab for locally advanced head and neck cancer.

Patients and methods. – From August 2006 and October 2010, 36 patients with advanced squamous cell head and neck carcinoma were treated with radiotherapy (70 Gy/35 fractions) and cetuximab (400 mg/m² one week before radiotherapy, following by 250 mg/m² once weekly, until week 7 of radiotherapy). Tolerance was evaluated every week. All patients were examined every 3 months the first 3 years after therapy, and then every year.

Results. – The median follow-up was 14 months. The majority of patients were male (31 out of 36). Mean age was 59 years. The tumours sites were: oral cavity ($n=8$); oropharynx ($n=15$); hypopharynx ($n=5$); larynx ($n=8$). Ninety percent of tumors were T3 or T4, and 45% were N2 or N3. Complete response was seen in 74% of patients, partial response in 17% and no response in 9% of patients. The overall survival was 44.4%. Relapse occurred in six patients. Anaphylactic reaction during the first infusion of cetuximab was observed in one patient. One patient developed severe aplasia after 48 Gy and 5 weeks of cetuximab, and died of sepsis. Eighty percent of patients presented acne, 16 patients developed a mucositis grade 2–3 and 23 patients a grade 2 skin reaction.

Conclusion. – The concomitant use of cetuximab and radiotherapy in locally advanced head and neck carcinoma is well tolerated in this group of patients. The results seem comparable to those in the literature.

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R É S U M É

Objectif de l'étude. – Décrire les résultats cliniques et la tolérance d'un traitement par irradiation et cetuximab (Erbix[®]) chez des patients atteints de carcinome épidermoïde de la sphère ORL localement évolué.

Patients et méthodes. – D'août 2006 au octobre 2008, 36 patients atteints d'un carcinome épidermoïde évolué de la sphère ORL de stade IV non métastatique ont bénéficié d'une association de radiothérapie de 70 Gy en 35 séances et de cetuximab (400 mg/m² la semaine précédant la radiothérapie puis 250 mg/m² chaque semaine de la radiothérapie). La tolérance a été évaluée chaque semaine. Tous les patients ont été examinés tous les trois mois les trois premières années après le traitement, puis tous les ans.

Résultats. – Le suivi médian était 14 mois. La majorité des patients étaient de sexe masculin (31 sur 36). L'âge moyen était de 59 ans. La localisation tumorale était la cavité buccale pour huit patients, l'oropharynx pour 15, l'hypopharynx pour cinq et le larynx pour huit. Quarante-vingt-dix pour cent des tumeurs étaient de stade T3 ou T4, et 45 % N2 ou N3. Une réponse complète a été observée chez 74 % des patients, une réponse partielle chez 17 % et pas de réponse dans 9 % des patients. La probabilité de survie globale était de 44,4 %. Une rechute est survenue chez six patients. Une réaction anaphylactique au cours

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de la première perfusion du cetuximab a été observée chez un patient. Un patient a souffert d'une aplasie sévère après 48 Gy et cinq semaines de cetuximab, et est décédé d'une septicémie. Quatre-vingt pour cent des patients ont été atteints d'acné, 16 d'une mucite de grade 2–3 et 23 d'une réaction cutanée de grade 2.

Conclusion. – Notre étude montre une bonne tolérance au traitement associant radiothérapie et cetuximab. Les résultats semblent comparables à ceux publiés dans la littérature.

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1. Introduction

Head and neck cancers are the sixth most common solid malignancies worldwide and are related to 350,000 deaths worldwide every year [1]. Most (90–95%) of head and neck cancers are squamous cell carcinomas (HNSCC). The most important risk factors for HNSCC are tobacco abuse and alcohol consumption, implicated in 75% of all HNSCC [1]. Recently, the human *papillomavirus* (HPV) infection has been implicated [2].

The management of patients with HNSCC is complex, owing to the heterogeneity of this disease [2].

Traditionally, the patients' managing with HNSCC has been surgical. Gradually the radio-chemotherapy has been included as an option, searching increased survival, curability, organ preservation and quality of life [3,4].

Knowledge of new molecules implicated in the cancer pathogenesis has led to the development of new therapeutic strategies. Between these, epidermal growth factor (EGF) has been described as an interesting target. The EGF receptor (EGFR) is a transmembrane glycoprotein possessing tyrosine kinase activity. The EGFR is abnormally activated in HNSCC, and overexpression of this receptor is associated with more aggressive disease [3].

Cetuximab is a chimeric human-murine immunoglobulin G1 monoclonal antibody highly selective for the EGFR [5].

Here we described the clinical results and tolerance of the combined treatment with radiotherapy and cetuximab in 36 HNSCC patients treated in the department of radiotherapy at the Brest University, France.

2. Patients and methods

Thirty-six HNSCC patients treated between August 2006 and October 2010 with combination of radiotherapy and cetuximab in the radiotherapy department of the Brest University Hospital, France, were retrospectively reviewed. Treatment tolerance and response were analyzed.

The patients were evaluated with endoscope, head and neck computed tomography (CT) and PET-scanner. Metastasis were not found. No prior treatment had been carried out. A gastrostomy was made in 22 patients. All patients underwent CT simulation where the gross tumour volume (GTV), clinical target volume (CTV) and the planning target volume (PTV) were defined. The first radiotherapy phase delivered a dose of 36 Gy with parallel opposed 6 MV photon fields to the primary tumour and the first echelon nodes, including the spinal cord.

To cover the lower neck and the supraclavicular nodes, one anterior portal was used; a prophylactic dose of 50 Gy at 3 cm depth was delivered. The second phase of treatment to the tumour involved a reduction in size of the field to bring the posterior border off the spinal cord. This phase delivered 14 Gy to the tumour. Asymmetric jaws were used to give minimum penumbra posteriorly, and an electron field was matched on to treat the upper posterior neck to 50 Gy total dose. A third phase of treatment used photon beams. A total dose of 70 Gy would be reached. Photon treatment was delivered using a Varian Clinac 2100C accelerator. Cetuximab dose was 400 mg/m² given one week before radiotherapy onset, then

Table 1

Distribution of the patients according the TNM-classification.
Répartition des patients selon la classification TNM (Union International Cancer Control-American Joint Committee on Cancer tumor, node, metastasis).

Location	Oral cavity 22.2% N	Oropharynx 41.8%	Larynx 22.2%	Hypopharynx 13.8%
Size	T1 5%	T2 14%	T3 25%	T4 55%
Lymph node invasion	N0 38%	N1 17%	N2 28%	N3 17%

250 mg/m² once weekly, until week 7 of radiotherapy. Tolerance was evaluated every week. The side effects are classified according the Radiation Therapy Oncology Group (RTOG) Score.

3. Statistical analysis

Survival and control response probabilities were calculated from the day of the end of radiotherapy. The results are expressed as mean $\pm$ standard deviation. Comparisons between means were performed by Mann-Whitney U test. The Kaplan-Meier method was used to determine overall survival (OS) and disease-free survival.

4. Results

Thirty-six HNSCC patients were treated with combined radiotherapy and cetuximab. All patients were available for assessment of tumour response, toxicity and disease-free survival. The median follow-up was 14 months. The majority of patients were male (31/36). Mean age was 59 years. Smoking history was present in 97% of cases, and alcohol consumption in 62% of patients. The tumours sites were the oral cavity ($n = 8$); oropharynx ($n = 15$); hypopharynx ($n = 5$); larynx ($n = 8$). Ninety percent were T3 or T4, and 45% were N2 or N3. The details are reported in the Table 1.

None patient presented a synchronous carcinoma. Three other patients had associated malignant disease (prostate cancer in one patient and lung adenocarcinoma in one patient). The mean weight for patients with gastrostomy was 67.25 kg at the beginning and 65.57 kg at the end of the treatment ($P = 0.85$). For patients without gastrostomy the weight was 66.85 kg at the beginning and 62.8 kg at the end of treatment ($P = 0.36$).

The Karnofsky Index was 80% or more in all patients.

Eighty-six percent of patients completed the radiotherapy treatment dose planned.

5. Follow-up

All patients were examined every 3 months the first 3 years after therapy, and then every year. They underwent clinical ENT-examination including magnifying laryngoscopy, ultrasound, PET-scan and/or a CT of the head and neck region if indicated.

6. Response and recurrence

The complete response was defined as the absence of recurrent disease above the clavicles and partial response as a decrease in

Table 2

Acute side effects of treatment in 36 HNSCC patients treated with radiotherapy and cetuximab.

Effets secondaires aigus chez 36 patients atteints de carcinome épidermoïde de la sphère ORL traités par irradiation et cetuximab.

Grades (RTOG)	Mucositis (%)	Skin (%)	Xerostomia (%)
0	0	0	14
1	55	29	50
2	40	66	33.3
3	5	5	2.7
4	0	0	0

the size of tumor and/or lymph node and was evaluated 2 months following the radiotherapy by clinical examination and CT scans. Complete response was seen in 74% of patients, partial response in 17% and no response in 9% of patients.

Death has occurred in 20 patients. In each case, the patient either died from carcinoma or had active disease at the time of death. OS was 44.4%.

Relapse occurred in six patients, the initial site of relapse being local (3), regional (1), as well as two cases of pulmonary metastasis (one associated with a local recurrence).

The median hemoglobin (Hb) level was 13.15 g/dl before treatment. There was not difference in the OS between the groups according to the Hb levels ($P=0.8$).

7. Toxicity

Anaphylactic reaction during the first infusion of cetuximab was observed in one patient. One patient developed severe aplasia the fifth week of cetuximab, and died of sepsis. Eighty percent of patients presented acne.

Acute toxicity is listed in Table 2. During treatment 16/36 patients developed a mucositis grade 2–3. Two patients were hospitalised for 14 and 20 days secondary to a lung infection, 1 patient was rested for 17 days owing to acute respiratory distress syndrome requiring tracheostomy, one patient for eight days owing to acute coronary syndrome and five patients two to four days owing to grade 3 radiation dermatitis. Four patients stopped the therapy because of performed status deterioration.

8. Discussion

The most important goal in HNSCC treatment is to achieve locoregional control. To try to improve the results of treatment of HNSCC, several approaches have been used over the years. Although many patients will develop distant metastases, locoregional control of tumours remains the major problem. Surgery and radiotherapy remain the main methods of treatment. Multiple clinical trials have demonstrated the ability of concurrent chemo-radiotherapy to improve survival [6].

However, the goal is not achieved by lack of compliance to chemo-radiotherapy owing to increased toxicity, particularly among patients with coexisting medical conditions and decreased performance status.

In our study, the OS was 44.4%. The 5-year overall survival reported by Bonner was 45.6% [7].

Tolerance of cetuximab-based treatment is better except acneiform rash and infusion related reactions [2,3]. Acneiform rash was presented in 80% of patients in our series, signaling the high frequency of this reaction. Similar result is reported in the literature [8].

In our study, the treatment with cetuximab did not exacerbate the common toxic effects associated with radiotherapy. This result is similar to the study published by Bonner et al. [5], which

shows that 52% of patients presented a mucositis grade 3–5 in the radiotherapy alone compared to 56% of combined treatment with cetuximab and radiation dermatitis grade 3–5 18% versus 23%, respectively.

The presence of adverse events is directly related to compliance to the therapy. In our study, the toxicity profile was associated with minor effects on the compliance, presented as a few days of pause or few cases of treatments stopped in sight to the good tolerance of this combined treatment.

In our series, 61% of patients received a nutritional supplement by gastrostomy tube, which allowed stability in weight and nutritional status of this subgroup of patients. The difference was not statistically significant compared to patients without gastrostomy. However, the later group has a tendency to a lower final weight. This result is probably related to patient's number.

Several studies have demonstrated a correlation between hypoxia and Hb level. A low level of Hb is associated with resistance to treatment and therefore, an adverse impact on prognosis. In our series, we found no difference in OS, which can be explained by the limited number of patients [9].

In our study, we describe two patients with a lung infection. The relationships with cetuximab cannot be established. Reports of pulmonary toxicity associated with cetuximab are rare. One case was reported by Chua et al. [10].

Concomitant use of cetuximab and radiotherapy has been well tolerated in this group of patients, which shows the feasibility of this treatment. The results seem comparable to those in the literature.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Authors' contributions: C.A. reviewed the patient data and drafted the manuscript. G.V., P.M. and E.L. helped the draft of the manuscript. O.P. participated in its concept design and helped the draft of the manuscript. All authors read and approved the final manuscript.

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