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High incidence of cetuximab-related infusion reactions in head and neck patients

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ABSTRACT

Background Cetuximab is crucial in the management of squamous cell carcinoma of the head and neck of patients. Grade 3–4 cetuximab-induced infusion reactions (CI-IRs) occur in 2% of patients with colorectal cancer. Despite the 2.7% CI-IR rate in the EXTREME trial, higher rates were reported in small series of patients with head and neck squamous cell carcinoma (HNSCC) (6%–18%). There is an urgent need to better appraise the natural history and the predictive factors for CI-IRs in patients with HNSCC exposed to cetuximab.

Methods The medical records from patients with HNSCC (n=428) treated by cetuximab at Gustave Roussy from January 2013 to December 2015 were reviewed. The impact of potential risk factors was analysed.

Results Out of 428 patients, 24 patients (5.4%) presented CI-IR, including grade 3–4 (95.7%); about 21% (5/24) requiring intensive care unit referral and quasi all occurred within the first cycle (21/24). In a multivariate analysis, the occurrence of grade 3–4 CI-IR was associated with tobacco and alcohol history (p=8.5e–3) and with prior allergy history (p=2.9e–3). CI-IRs tended to be associated with poor overall survival in patients with recurrent and metastatic HNSCC and with a higher number of further lines of chemotherapy.

Conclusion In real life, CI-IRs appear far more common in patients with HNSCC (5.4%) than reported in prospective trials. This is the largest series of patients ever focusing on the risk of CI-IR in patients with HNSCC. Prior allergy history and tobacco history are associated with CI-IR and could be used to better allocate treatment. Further prospective data are required to confirm these findings.

Key messages

- ► Cetuximab is considered as a cornerstone of treatment in patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC). Several small series previously reported a higher rate of cetuximab induced infusion reaction (3%–8%) in HNSCC compared with a lower rate in the colorectal setting (0.5%).
- ► In this manuscript, we describe, in a large series of consecutive patients with HNSCC (n=428 patients) that cetuximab induced infusion reaction is far more common in patients with HNSCC in real life (5.4%) than reported in prospective trials. In addition, most of these events were severe (95.7%) and some of them required intensive care unit referral (20%).
- ► Interestingly, we found an association with both prior alcohol/tobacco exposure and allergy history that could explain the difference in the incidence observed between the colorectal and the HNSCC settings.
- ► More importantly, the latter findings could allow the bedside oncologist to better identify patients more prone to present cetuximab-induced infusion reaction.
- ► On clinical practice, this could help the bedside oncologist to adapt the surveillance of patients with HNSCC eligible to cetuximab.

INTRODUCTION

Cetuximab is a chimeric human-murine monoclonal antibody that binds competitively and with high affinity the epidermal growth factor (EGFR), blocking ligand binding, resulting in inhibition of the receptor function. It also triggers cytotoxic immune effector cells towards EGFR-expressing tumour cells through antibody-dependent cell-mediated cytotoxicity.[1] Cetuximab is crucial in the management of patients with squamous cell carcinoma of the head and neck (HNSCC).[2–5] In the locally advanced setting, the addition of cetuximab to radiotherapy (RT) improves locoregional control and survival when compared with RT alone.[3] In the recurrent or metastatic setting, the EXTREME regimen (cisplatin, 5FU, cetuximab) also demonstrated an improvement in overall survival over the platinum-5FU combination.[4]

Among the adverse events (AEs) frequently observed following cetuximab administration, the occurrence of cetuximab-induced infusion reaction (CI-IR) appears difficult to predict and to manage. Despite the 2.7%

Table 1 Descriptive statistics

	CI-IR (n=24) N	No CI-IR (n=404) N	P values (Fisher's exact test)
Localisation			0.35
Oropharynx	10	184	
Hypopharynx	3	72	
Larynx	5	71	
Oral cavity	6	50	
Other	0	27	
Disease stage			0.08
Locally advanced disease	6	180	
Recurrent or metastatic disease	18	224	
Gender			0.06
Female	1	79	
Male	23	325	
Allergic history			0.037
Yes	8	60	
No	16	344	
Tobacco history			6e–4
Yes	24	290	
No	0	114	
Alcohol history			5e–3
Yes	21	240	
No	3	164	
Combined tobacco and alcohol history			1e–3
Yes	21	220	
No	3	184	
Previous chemotherapy			NS
Yes	10	111	
No	14	141	
Previous radiotherapy			0.65
Yes	6	76	
No	18	167	
Baseline lymphocyte counts	900 (0–5400)	1000 (200–3900)	0.68*
Baseline eosinophils counts	100 (0–900)	100 (0–1300)	0.73*

*Wilcoxon test p value.
CI-IR, cetuximab-induced infusion reaction.

infusion reaction (CI-IR) rate in the EXTREME trial, higher frequencies were further reported in small series of HNSCC (6%–18%).[6 7] Interestingly, this AE appears rare in patients with colorectal cancer (CRC) (2% grade 3–4 IR in the ASPECCT trial, n=500 patients).[8]

Further, the fact that many CI-IRs occurred within minutes after the first exposure to the drug prompted the hypothesis of an IgE-mediated anaphylaxis mechanism. IgE specific for Galactose-α–1,3-Galactose have been demonstrated to predict the occurrence of CI-IR.[9] However, this test is rarely used in clinical practice.

There is an urgent need to better appraise the natural history and the predictive factors for CI-IRs in HNSCC patients. This study aims to investigate the occurrence of CI-IRs and their associated factors in a large series of patients with HNSCC treated with Cetuximab.

MATERIAL AND METHODS
Patients
All consecutive patients with locally advanced, recurrent/metastatic HNSCC (n=428 patients) treated with Cetuximab from January 2013 to December 2015 at Gustave Roussy were analysed. The following clinical and pathological variables were extracted: age, gender, date at diagnosis, date of treatment onset, primary tumour location,

Table 2 Multivariate logistic regression model of CI-IR in patients with HNSCC

	Estimate	P values
Intercept	−4.48	<1e−5
Combined tobacco or alcohol history	1.24	8.5e−3
Allergic history	1.88	2.9e−3

CI-IR, cetuximab-induced infusion reaction; HNSCC, head and neck squamous cell carcinoma.

HPV status (estimated by P16 IHC expression), treatment type, allergy history, eosinophils and lymphocytes rate before the administration of Cetuximab, tobacco and alcohol history. The occurrence of cetuximab induced infusion reactions (CI-IRs) was recorded (date, treatment cycle, severity as per NCI-CTC-AE V.4.0,[10] associated measures). Finally, the outcome of the patients was also analysed: number of consecutive treatment lines, overall survival.

Cetuximab-based regimen and premedications
All patients analysed received premedication including corticosteroids and antihistamines (H1 antagonist).

Patients who were treated by the EXTREME protocol[2] received 120 mg of intravenous methylprednisolone and 5 mg of intravenous dexchlorpheniramine before first day of cetuximab (initial dose of 400 mg/m² intravenously followed by 250 mg/m² intravenously) and only 5 mg of intravenous dexchlorpheniramine without corticosteroids before the day 8 and 15 of cetuximab (250 mg/m² intravenously). Treatment with cetuximab continued until disease progression, intolerability or withdrawal of consent.

In the group of patients who received RT plus cetuximab,[6] administration of intravenous cetuximab was initiated 1 week before RT at a loading dose of 400 mg/m², followed by weekly infusions of 250 mg/m² for the duration of RT. Premedication consisted of intravenous diphenhydramine (50 mg) or an equivalent histamine H_1–receptor antagonist before each dose and 120 mg of intravenous methylprednisolone before the first dose and 60 mg before the next doses.

Table 3 Probability of CI-IR according to the variables tobacco and alcohol history, allergy history and the combination of them

Tobacco and allergy history, n (%)	Allergy history, n (%)	CI-IR, n (%)
No	No	2/152 (1%)
No	Yes	1/35 (2.8%)
Yes	No	14/208 (6.7%)
Yes	Yes	7/33 (21.7%)

CI-IR, cetuximab-induced infusion reaction.

Management of CI-IR
Infusion was immediately suspended for any grade of infusion reaction. Dosing could be resumed for National Cancer Institute Common Toxicity Criteria (NCI CTC AE V.4.0[10]) with a 50% infusion-rate reduction for grade 1 (transient flushing or rash, no fever) or 2 (flushing, urticaria, rash and fever up to ≥100.4°F) reactions but was permanently discontinued for grade 3–4 reactions (rapid onset of bronchospasm, stridor, hoarseness, nausea and vomiting, urticaria and/or hypotension) requiring medical intervention and/or hospitalisation. Gustave Roussy's health personnel have a continuing education programme for IR and Cardiopulmonary resuscitation. On onset of a CI-IR (grades 1–4), cetuximab administration was stopped and intravenous fluids and supplemental oxygen were administered as needed. Additionally appropriate medical treatment of CI-IRs was delivered with H1-blockers, corticosteroids, H2-blockers, inhaled nebulised albuterol or epinephrine.[11–13] Patients should be carefully observed until the resolution of all symptoms and signs. Cetuximab rechallenge was avoided in our patients following a severe infusion reaction.

RESULTS
Prevalence and natural history of CI-IR in patients with HNSCC
Out of a total of 428 consecutive patients with HNSCC, we observed CI-IRs in 24 patients (5.4%) including grade 3–4 for patients with CI-IR (95.7%), according to the NCI-CTC AE V.4.0 guidelines[10] and five patients required a transfer in the intensive care unit. The main clinical characteristics of the patients are described in table 1. Importantly, quasi all the CI-IRs occurred during the first cycle (87.5%, 21 patients), while two CI-IRs occurred during the second cycle and one during the third cycle.

Associated clinical and pathological variables with CI-IR
In univariate analyses, the occurrence of CI-IR was associated with prior allergy history (Fisher's exact test, p=0.037), alcohol consumption history (Fisher's exact test, p=5e−3) and tobacco history (Fisher's exact test, p=6e−4). However, no association was observed between CI-IR and tumour location (Fisher's exact test, p=0.35), previous RT (Fisher's exact test, p=0.8) or chemotherapy (Fisher's exact test, p=NS), with the baseline eosinophils or lymphocytes count (Wilcoxon test, p=0.73 and p=0.68, respectively) (table 1). It is well known that alcohol and tobacco exert a synergistic effect on the oncogenesis of HNSCC. Consecutively, a great proportion of patients with HNSCC present a combined tobacco and alcohol history. In our series, we observed that the occurrence of CI-IR was strongly associated with combined tobacco and alcohol history (Fisher's exact test, p=1.2e−3).

Interestingly, the variables combined tobacco and alcohol history (OR=1.88, p=2.9e−3) and allergy history (OR=1.24, p=8.5e−3) remained highly significantly associated with the occurrence of grade 3–4 CI-IR in a multivariate logistic regression model (table 2).

Table 4 Overall survival according to the CI-IR status in patients with HNSCC (locally advanced disease and recurrent or metastatic disease)

		Overall survival median, (95% CI)	Log rank test
Patients with locally advanced disease HNSCC treated by cetuximab potentiated chemoradiation	CI-IR, n=6	42.9 (5.3 to NA) months	0.51
	No CI-IR, n=180	22.6 (16.0 to 46.0) months	
Patients with recurrent or metastatic disease HNSCC treated by cetuximab-based systemic chemotherapy	CI-IR, n=18	6.5 (5.4 to NA) months	0.17
	No CI-IR, n=223	12.7 (11.1 to 16.2) months	

CI-IR, cetuximab-induced infusion reaction; HNSCC, head and neck squamous cell carcinoma.

For more clinical relevance, we computed in our cohort the risk of developing CI-IR according to the significant variables taken alone or combined (table 3). Patients with neither combined tobacco and alcohol history nor allergy history had a 1% (2 out of 152 patients) risk of developing CI-IR. Patients with combined tobacco and alcohol history but no allergy history had a 6.7% (14 out of 208 patients) risk of developing CI-IR. Patients with allergy history but no combined tobacco and alcohol history had a 2.8% (1 out of 35 patients) risk of developing CI-IR. Patients with both combined tobacco and alcohol history and allergy history had a 21.2% (7 out of 33 patients) risk of developing CI-IR.

Clinical consequences of CI-IRs

We investigated the impact on the outcome of CI-IR (1) in patients with locally advanced disease treated by cetuximab based radiochemotherapy and further (2) in patients with metastatic treatment treated by cetuximab-based chemotherapy (table 4). We observed that CI-IR tended to be associated with worse overall survival in patients with recurrent and metastatic HNSCC, although no significant difference was observed in the two groups. In locally advanced patients, the median

overall survival HNSCC patients presenting CI-IR was 42.9 months (95% CI (5.3-NA)) vs 22.6 months (95% CI (16.0 to 46.0)) for those who did not present CI-IR. In patients with recurrent or metastatic (RM), the median overall survival of patients with HNSCC with CI-IR was 6.5 months (95% CI (5.4-NA)) vs 12.7 months (95% CI (11.1 to 16.2)) for those who did not present CI-IR (figure 1).

Finally, we investigated the influence of CI-IR on the number of further lines of chemotherapy in R/M disease. As expected, we observed that patients with CI-IR required a higher number of lines of treatment following the first line of cetuximab based chemotherapy (Fisher's exact test, p=2.2e−3) (table 5, figure 2).

DISCUSSION

To our knowledge, this is the largest series ever exploring the risk of CI-IR in patients with HNSCC in real life (n=428 patients). CI-IR occurs in 5.4% patients with HNSCC and mostly during the first cycle. They usually become severe (95.7% grade 3–4) and cause fatal outcomes if not managed appropriately.
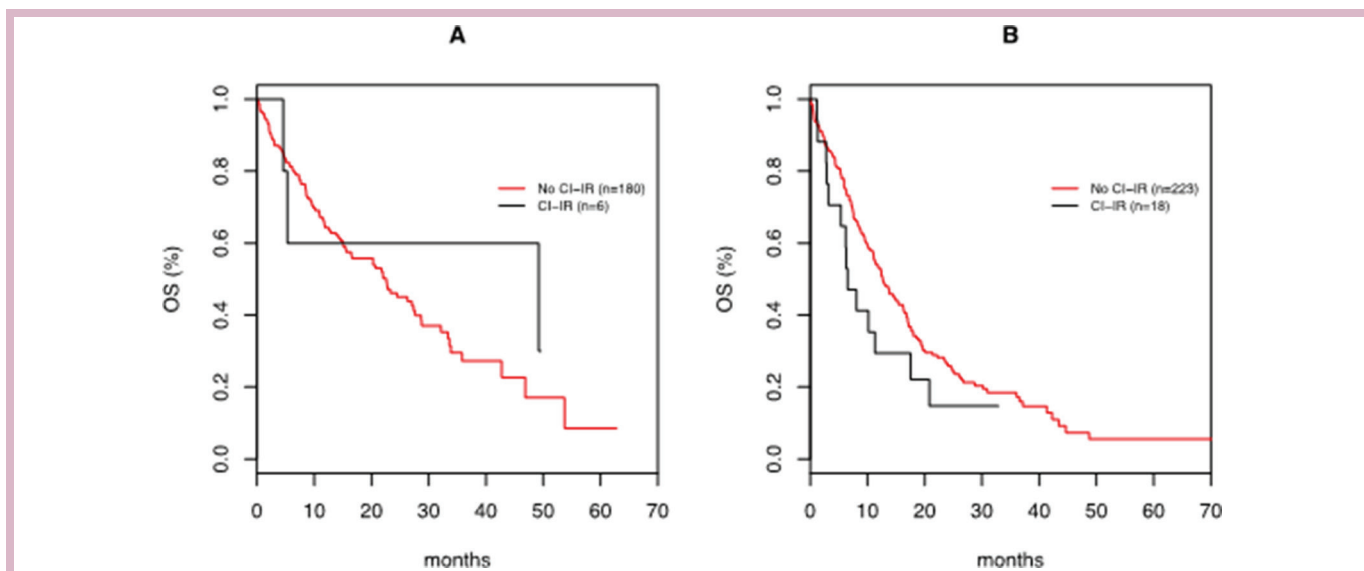

Figure 1 Overall survival according to the CI-IR status in patients with HNSCC. Panel A: patients with locally advanced disease treated by cetuximab-potentiated chemoradiation (n=186). Panel B: patients with recurrent or metastatic disease treated by systemic chemotherapy (n=241). CI-IR, cetuximab-induced infusion reaction; HNSCC, head and neck squamous cell carcinoma.

Table 5 Distribution of the total number of chemotherapy lines after the first line of cetuximab-based systemic treatment in recurrent or metastatic patients (n=241)

Number of chemotherapy lines after cetuximab-based systemic treatment	CI-IR (n=18)	No CI-IR (n=223)	P values (Fisher's exact test)
0	4 (22.2%)	140 (62.7%)	2.2e–3
1	7 (38.9%)	49 (22.0 %)	
2	6 (33.3%)	24 (10.8%)	
3+ (3 or more)	1 (5.6%)	10 (4.5%)	

CI-IR, cetuximab-induced infusion reaction.

Our findings are consistent with previous retrospective data (6%–7% CI-IR).[3 4] A retrospective chart review included 153 patients that received cetuximab at the Oklahoma University Health Sciences Center.[3] The overall incidence proportion of severe hypersensitivity infusion reactions was 12.4% and current smokers had an increased incidence of severe hypersensitivity infusion reactions of 23.6%, p=0.0012. Another retrospective chart review with 72 patients treated at the Duke University's Morris Oncology treatment center[4] confirms a high rate of cetuximab hypersensitivity reactions; 18% experienced reactions grades 3 or 4 and patients with head and neck cancer significantly more than patients with colon cancer. In addition, in patients with CRC, the ASPECCT study only encounters 2% of anaphylactic reaction.[1] Another retrospective study in Japan with 248 patients reported an all grade CI-IR of 5.2%.[12] A robust retrospective study of 243 patients showed an overall risk of CI-IR (grades 1–4) of 19.3% whose 6.6% with a high grade CI-IR.13 However, in a recent retrospective study, global CI-IR rate was among 20%.[13] This rate can

Figure 2 Distribution of the number of lines postcetuximab-based chemotherapy in patients with recurrent or metastatic HNSCC (n=241 patients). CI-IR, cetuximab-induced infusion reaction.

be explained by the demographic region with a risk of high tick bites and therefore cross allergy with cetuximab, that is not the case in our study because we are in urban area.

Premedications were conducted as recommended by the latest international guidelines. Interestingly, premedications are the same for patients with CRC and HNSCC. Thus, this does not explain the difference of prevalence observed between these two cancer types. Given our results of high grade CI-IRs (95.7%), we could discuss the choice of the premedication. In fact, it was showed that additional premedication like albuterol, famotidine and corticosteroids decreases high grade CI-IRs.[13]

Some retrospective studies reveal an association between some risk factors and CI-IR,[14–16] but our is the largest study.

We found that tobacco and alcohol history and prior allergy history are strongly associated with CI-IR in patients with head and neck cancer. The combination of these two variables leads to up to 22% patients with CI-IRs. The tobacco and alcohol exposure is well recognised as a strong oncogenic driver of HNSCC. This could therefore explain the difference of prevalence of CI-IR observed in patients with HNSCC versus CRC. The tobacco and alcohol exposure could mediate local chronic inflammation and favour an IgGE mediated reaction.

Cetuximab is produced in the mouse cell line SP2/0, which expresses the gene for α–1,3-galactosyltransferase which resulting in the expression of a Galactose-α–1,3-Galactose structure on the Fc part of the antibody. Naturally, people can develop IgE specific for Galactose-α–1,3-Galactose and it has have been associated with cetuximab infusion reaction.[9] Blood analyses used to detect the presence of IgE anti Galactose-α–1,3-Galactose could help in better identifying high risk patients but its implementation in clinical practice is difficult and yet not validated in large series.[17] Waiting for more performing biomarkers, the identification of tobacco and alcohol history and of priori allergy history could help to better allocate the treatment and the surveillance of patients with HNSCC eligible to cetuximab.

Patients with grade 3 CI-IR were not rechallenged with cetuximab because of poor data available with this grade.[13]

Our study is though limited by several flaws. Particularly, the fact that our analyses are retrospective and based on a single institution recruitment limit the generalisability
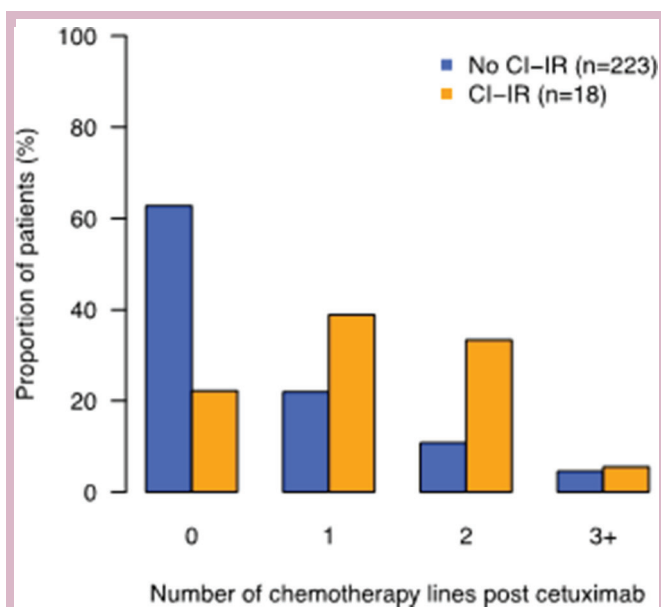
of our results. Further prospective data are, however, required to confirm these findings.

Unfortunately, these are retrospective data for OS and we did not report the Overall Response Rate that it requires a centralised analysis which is in progress.

In real life, CI-IRs appears far more common in patients with HNSCC (5.4%) than reported in prospective trials. This is the largest series of patients ever focusing on the risk of CI-IR in patients with HNSCC. Alcohol and tobacco history and prior allergy history were strongly associated with CI-IR and could help bedside oncologist to adapt the surveillance of patients with HNSCC eligible to cetuximab.

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