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J Oncol Pharm Pract published online 15 November 2012

DOI: 10.1177/1078155212457965

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Cetuximab infusion reactions: French pharmacovigilance database analysis

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Abstract

Objectives: To compare characteristics of patients exhibiting cetuximab infusion reactions or another adverse drug reaction related to cetuximab and to identify factors associated with the severity of cetuximab infusion reactions.

Methods: All cases of adverse drug reaction reported with cetuximab from 1985 to 2010 were extracted from the French Pharmacovigilance database. The severity of infusion reactions was assessed according to the NCI-CTCAE criteria (v4.0). Multiple logistic regression analysis was performed to identify factors associated with the severity of infusion reactions.

Results: Among the 602 adverse drug reaction reported with cetuximab during the study period, 374 infusion reactions were identified. Indication is more likely to be head and neck than colorectal cancer among patients experiencing an infusion reaction ($p < 0.001$). Among the seven deaths related to an infusion reaction, five patients were treated for head and neck cancer. Infusion reactions were more likely to be severe when they occurred during the first administration (OR = 7.40 95% CI [2.21–24.71]), adjusted for age, sex, region of France, quarter of the year, indication, year of occurrence, and premedication.

Conclusion: Our study found that reports of infusion reactions more often concerned patients treated for head and neck cancer, that in these patients the adverse drug reaction was more often fatal and severe infusion reactions were more likely during the first administration. In daily practice, the close monitoring of patients during the first infusion, especially patients with head and neck cancer, is recommended. Considering the possible immunoglobulin E-mediated mechanism, reliable tests for their detection need to be readily available.

Keywords

Cetuximab, infusion reaction, severity, hypersensitivity

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Introduction

Cetuximab (Erbix[®], Merck Serono) is a chimeric monoclonal antibody authorised in Europe in 2004 for metastatic colorectal cancer and in 2006 for squamous cell carcinoma of the head and neck. It is an immunoglobulin G1k, produced by the Sp2/0 murine myeloma cell line (ImClone Systems), which binds to epidermal growth factor receptor (EGFR) with a high affinity and blocks ligand-induced phosphorylation of the receptor.^{1,2}

Among the side effects of cetuximab, infusion reactions have frequently been observed. Mild or moderate symptoms may include fever, chills, dizziness, or dyspnoea. Severe reactions may include symptoms such as bronchospasm, urticaria, increase or decrease in blood pressure, loss of consciousness, or shock.¹ The rate of severe reactions is between 1% and 10% according to the European Summary of Product Characteristics (SPC).¹ ImClone product information indicated a proportion of severe reaction between 2% and 5% of 1373 patients in 4 studies, with fatal outcome in 1 patient.²

Symptoms most often occurred during the first infusion and up to 1 hour after the end of the infusion, but may also occur after several hours or with subsequent infusions.¹ Regarding the mechanism of these reactions, the SPC indicates that "Although the underlying mechanism has not been identified, some of these reactions may be anaphylactoid/anaphylactic in nature."¹

Initially, considering the time to onset (over 90% occurred in the first cycle), the assumption of an anaphylactic mechanism mediated by immunoglobulin E (IgE) was not the most likely.³ However, a retrospective study in USA showed the presence of IgE antibodies directed against cetuximab in the serum of some patients prior to treatment with cetuximab.⁴

Risk factors of infusion reactions have not been clearly elucidated. A study conducted in the USA reported an association between Caucasians and the occurrence of hypersensitivity reactions.⁵ No association was found with age and sex. In another study, O'Neil et al. found no association between the severity of such reactions and age, gender, ethnicity or type of cancer.⁶ However, an association between severity of these reactions and a history of atopy was found.

In a study conducted in North Carolina, an association was found between the indication for head and neck cancer and the occurrence of a hypersensitivity reaction.⁷ Another study found an association with non-small-cell lung cancer.⁶

Given these sparse data and the lack of European studies, we set up a study using data from the French Pharmacovigilance Database to compare the characteristics of patients presenting with an infusion reaction related to cetuximab with those of patients with other

adverse reactions (ARs) with cetuximab and to identify factors associated with the severity of infusion reactions.

Methods

Source of data

Data were extracted from the French Pharmacovigilance Database (which includes all adverse drug reactions (ADR) reported to and validated by the 31 French Pharmacovigilance Centers) between 1 January 1985 and 31 December 2010. The relationship between an AR and a drug was assessed according to the French pharmacovigilance causality assessment method.⁸ Five levels are defined: I0 (excluded), I1 (doubtful), I2 (possible), I3 (likely), I4 (very likely). The seriousness of each case was recorded according to the regulatory definition⁹: a case is considered serious when it results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, a congenital anomaly/birth defect or other situations that may require intervention to prevent one of the other outcomes listed above. All reactions are coded according to MedDRA.¹⁰ For the present study, all cases of ARs related to cetuximab with a causality assessment level different from I0 (i.e. I1, I2, I3 or I4) were considered.

Each infusion reaction report was reviewed by a Pharmacovigilance specialist (AG). An infusion reaction was validated if the first symptom (cutaneous, respiratory, hemodynamic, digestive, etc.) occurred within a few seconds to 24 hours after the start of the administration of cetuximab. Twenty-four hours is the time to onset for the longest infusion reaction mentioned in the SPC of different monoclonal antibodies for which time to onset was reported.^{11,12}

Exclusion criteria were duplicate reports; reports in which causality assessment for drugs other than cetuximab was higher than that for cetuximab; reports for which ADRs concerned the nurse who administered the drug.

The severity of each reported infusion reaction was assessed by referring to the criteria of the National Cancer Institute (CTCAE) version 4.0.¹³ The term "Allergic reaction" or "Anaphylaxis" of the organ class "Immune system disorders" was considered (Table 1). The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE that could be condense as follows: grade 1 (mild), grade 2 (moderate), grade 3 (severe), grade 4 (life-threatening), and grade 5 (death). Taking into account the medical relevance of the severity of infusion

Table 1. Common terminology criteria for adverse events terms used for grading infusion reaction (NCI CTCAE v4.0).

Immune System Disorders					
Grade					
Adverse event	1	2	3	4	5
Allergic reaction	Transient flushing or rash, drug fever <38°C (<100.4°F); intervention not indicated	Intervention or infusion interruption indicated; responds promptly to symptomatic treatment (e.g. anti-histamines, NSAIDs, narcotics); prophylactic medications indicated for ≤24 h	Prolonged (e.g. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (e.g. renal impairment, pulmonary infiltrates)	Life-threatening consequences; urgent intervention indicated	Death
Anaphylaxis	—	—	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.					

reactions, we considered reactions grade 1 to 3 non-severe and grade 4 and 5 severe.

Statistical analysis

Characteristics of patients and adverse drug reactions were described using percentages for categorical variables and means and standard deviations for continuous variables. Comparisons were made by Chi-square or Fisher's exact test for categorical variables.

Severity was considered the dependent variable for the analysis. Associations between the potential risk factors and the seriousness of the infusion reaction were first assessed with univariate logistic regression. Age (split into 2 categories: <65 or ≥ 65 years), sex, and potential risk factors associated with the dependent variable in the univariate analysis with $p \leq 0.25$ were introduced into a multivariate logistic model. A backward stepwise procedure was used to identify variables independently associated with the dependent variable and the final model was tested for interactions. The level of significance used for the tests was $p < 0.05$. All analyses were conducted using SAS version 9.1 (SAS Institute Inc., North Carolina, USA).

Results

The initial query from the database identified 634 ADR reports. Thirty-two reports were excluded. The remaining 602 reports were divided into two groups: "Infusion reactions" ($n = 374$) and "other adverse reactions (AR)" ($n = 228$).

The characteristics of infusion reactions and other AR are reported in Table 2.

The proportion of serious reports was higher for infusion reactions than for other AR ($p < 0.001$). The proportion of females was higher in the other-AR group ($p < 0.001$). Age, region of occurrence, and quarter of the year of occurrence were similar in the two groups. Reports of infusion reactions increased between 2004 (first report) and 2011 ($p < 0.001$), while those of other ARs remained relatively stable. In cases of infusion reactions, cetuximab was more often indicated for head and neck cancer than for colorectal or other cancers ($p < 0.001$). Infusion reactions were more likely than other ARs to occur during the first cycle (66.8% vs. 34.6%), while the inverse was true for cycle 2 or more (10.2% vs. 57.0%) ($p < 0.001$).

The analysis of infusion reaction reports showed that the majority (71.4%) of infusion reactions occurred during the first half of the infusion, with a significant imbalance between non-severe (66.3%) and severe (80.9%) cases ($p = 0.003$) (data not shown). Based on the 217 cases where the time to onset was

Table 2. Characteristics of cases of infusion reactions related to cetuximab and other adverse reactions related to cetuximab recorded in the French pharmacovigilance database between 1 January 1985 and 31 December 2010.

	Infusion reactions N = 374	Other adverse reactions N = 228	p Value
Age n (%)			0.479
<65	212 (56.7)	133 (58.3)	
≥65	162 (43.3)	90 (39.5)	
Sex n (%)			<0.001
Male	305 (81.5)	152 (66.7)	
Female	69 (18.5)	76 (33.3)	
Region n (%)			0.029
North East	78 (20.9)	43 (18.9)	
South East	60 (16.0)	46 (20.2)	
South West	107 (28.6)	48 (21.0)	
North West	69 (18.4)	35 (15.3)	
Paris	60 (16.0)	56 (24.6)	
Year n (%)			<0.001
2004	19 (5.1)	33 (14.5)	
2005	14 (3.7)	36 (15.8)	
2006	32 (8.6)	23 (10.1)	
2007	45 (12.0)	26 (11.4)	
2008	67 (17.9)	51 (22.4)	
2009	100 (26.7)	44 (19.3)	
2010	97 (25.9)	12 (5.3)	
Trimester n (%)			0.327
Jan–Mar	86 (23.0)	59 (25.9)	
Apr–Jun	76 (20.3)	46 (20.2)	
July–Sept	104 (27.8)	70 (30.7)	
Oct–Dec	106 (28.3)	49 (21.5)	
Indication n (%)			<0.001
Colorectal	145 (38.8)	156 (68.4)	
Head and neck	155 (41.4)	44 (19.3)	
Other	28 (7.5)	18 (7.9)	
Unknown	46 (12.3)	10 (4.4)	
Cycle n (%)			<0.001
1 st	250 (66.8)	79 (34.6)	
≥2	38 (10.2)	130 (57.0)	
Seriousness n (%)			<0.001
Serious	292 (78.1)	106 (46.5)	
Hospit./prolong. hospit.	154 (41.2)	60 (26.3)	
Life-threatening	100 (26.4)	16 (7.0)	
Death	7 (1.9)	11 (4.8)	
Disability/incapacity	1 (0.3)	9 (3.9)	
Important medical event	29 (7.7)	9 (3.9)	
Serious without precision	1 (0.3)	1 (0.4)	
Non-serious	82 (21.9)	122 (53.5)	

indicated precisely, the average time to onset of infusion reactions was 22 minutes (median 15 minutes).

In 76.2% of reports, symptomatic treatment was administered after discontinuation of cetuximab: antihistamines and/or corticosteroids (59.6%), adrenaline intravenously (16.3%), oxygen and/or aerosols (25.9%), fluids/macromolecules (15.2%), other symptomatic treatment such as paracetamol or antiemetics (12.6%). In 9.1% of reports, no symptomatic treatment was necessary.

Cetuximab was reintroduced in 52 cases (13.9%). In 16 cases, reintroduction was done the day of the initial reaction, in 18 cases 1 week later, and in 6 cases 2 weeks later. The severity of the initial reaction was grade 1 in 2 cases, grade 2 in 5 cases, grade 3 in 39 cases, and grade 4 in 6 cases. Infusion reactions reappeared in 23 cases (44.2%). In 9 cases, the reintroduction led to a more severe reaction (from grade 3 to grade 4). Among the 29 cases with a reaction-free reintroduction, premedication was increased in 10 cases: corticosteroid added to the antihistamine (given alone before the first administration) in 6 cases; corticosteroid dose increased in 2 cases; other antihistamine given in 1 case; and premedication administered for 3 days before reintroduction in 1 case. In 9 other cases, the infusion rate was decreased (halved in 6 cases while the first administration was based on the SPC guideline which is 5 mL/min).

Among the 374 reports of infusion reactions, 243 (65.0%) were classified as non-severe (1.3% grade 1, 10.2% grade 2, 53.5% grade 3) and 131 as severe (35.0%) (33.2% grade 4 and 1.9% grade 5).

After univariate analysis (Table 3), the severity of the infusion reaction was no different according to the premedication in bi- or monotherapy (bithérapie vs. monothérapie OR = 1.26 CI 95% [0.65–2.43]), or the indication ($p = 0.252$).

In multivariate analysis, severe infusion reactions were more likely to occur during the first cycle (cycle 1 vs. cycle 2 or more OR = 7.40 CI 95% [2.21–24.71], $p = 0.005$) after adjustment for age, sex, region of France, quarter of the year, indication, and year of occurrence and premedication.

A fatal outcome (grade 5) was reported in 13 cases, including 7 directly related to the infusion reaction and 4 where the latter may have contributed to the death. Two deaths were not considered to be related to the infusion reaction. No deaths were found in other-AR reports.

Of the 7 deaths related to the reaction, 5 patients were treated for head and neck cancer and 1 for colorectal cancer (1 unknown). The reaction occurred in the first cycle for five cases (two unknown). Premedication consisted of a corticosteroid and antihistamine in 4 cases and monotherapy in 1 case (1 unknown).

Table 3. Univariate comparison of infusion reactions related to cetuximab in the French Pharmacovigilance database according to their severity.

	Non-severe (grade I–III) N = 243	Severe (grade IV–V) N = 131 (%)	Odds ratio [CI 95%]	P Value
Age n (%)				0.413
<65	134 (55.1)	78 (59.5%)	1.0	
≥65	109 (44.9)	53 (40.5%)	0.83 [0.54–1.28]	
Sex n (%)				0.151
H	193 (79.4)	112 (85.5%)	1.0	
F	50 (20.6)	19 (14.5%)	0.65 [0.37–1.17]	
Indication n (%)				0.252
Colorectal	93 (38.3)	52 (39.7%)	1.0	
Head & Neck	96 (39.5)	59 (45.0%)	1.10 [0.69–1.76]	
Other	22 (9.0)	6 (4.6%)	0.49 [0.19–1.28]	
Region n (%)				0.121
North East	49 (20.2)	29 (22.1%)	1.0	
South East	41 (16.9)	19 (14.5%)	0.78 [0.38–1.60]	
South West	74 (30.4)	33 (25.2%)	0.75 [0.41–1.39]	
North West	36 (14.8)	33 (25.2%)	1.55 [0.80–2.99]	
Paris	43 (17.7)	17 (13.0%)	0.67 [0.32–1.38]	
Year n (%)				0.404
2004	12 (4.9)	7 (5.3)	1.0	
2005	6 (2.5)	8 (6.1)	2.28 [0.56–9.36]	
2006	21 (8.6)	11 (8.4)	0.90 [0.27–2.93]	
2007	30 (12.3)	15 (11.4)	0.86 [0.28–2.62]	
2008	44 (18.1)	23 (17.6)	0.90 [0.31–2.59]	
2009	60 (24.7)	40 (30.5)	1.14 [0.41–3.15]	
2010	70 (28.8)	27 (20.6)	0.66 [0.23–1.86]	
Trimester n (%)				0.710
Jan–Mar	56 (23.0)	30 (22.9)	1.0	
Apr–Jun	53 (21.8)	23 (17.6)	0.81 [0.42–1.57]	
Jul–Sept	67 (27.6)	37 (28.2)	1.03 [0.57–1.87]	
Oct–Dec	65 (26.7)	41 (31.3)	1.18 [0.65–2.13]	
Cycle n (%)				0.001
Ist	153 (62.9)	97 (74.0)	1.0	
≥2	35 (14.4)	3 (0.02)	0.13 [0.04–0.45]	
Premedication				0.406
Monotherapy	46 (18.9)	19 (14.5)	1.0	
Bitherapy	75 (30.9)	39 (29.8)	1.26 [0.65–2.43]	
None	1 (0.4)	2 (1.5)	4.84 [0.41–56.63]	

In 4 cases, the death occurred despite resuscitation and administration of epinephrine. In one case, the patient died following acute pulmonary oedema with heart failure. One patient presented two successive cardiac arrests, the second was fatal.

Among the four deaths where the infusion reaction may have contributed to the death of the patient, the indications were head-neck in 3 cases and colorectal in

1 case. The causes of death were probable pulmonary embolism (death 2 hours after the initial reaction, which had completely resolved); disseminated intravascular coagulation in the aftermath of cardio-respiratory arrest (death within 12 hours following the initial reaction); multiple organ failure 11 days after the initial reaction that led to heart failure; and pulmonary infection acquired under mechanical ventilation

(death 27 days after the initial reaction which required intubation).

Discussion

We found that 62% of adverse events related to cetuximab recorded in the French Pharmacovigilance Database until 31 December 2010, were infusion reactions. The characteristics of these ARs were comparable to current data (literature and Erbitux® SPC). Most of the infusion reaction reports in our study were serious and severe. This was potentially related to the more spontaneous reporting of serious or severe ARs.

Our study population consisted of 76% men, which is consistent with the target population of cetuximab in its official statements. Indeed, head-neck cancers occur predominantly in males (80% of new cases in France are men¹⁴), colorectal cancer also affects men (55% in a population-based study carried out in two French departments¹⁵). This result is also consistent with the data provided by the Agence de Traitement de l'Information Hospitalière (ATIH) (involving French Public Hospitals and private health-care institutions): over the period 2009–2010, 70.4% of patients treated with cetuximab were men.¹⁶ In our study, infusion reactions seemed to be more likely in males, but the indication was probably a confounding factor as shown in a previous study.⁷ Nevertheless, sex could have an impact as males were also more likely to have a history of atopy.¹⁷

We found no association between the severity of infusion reactions and age, which is consistent with results from other studies^{5–7} or with the region of occurrence (unlike in the USA⁴). We found no evidence of seasonality that could have correlated with periods associated with environmental allergies (spring), as atopy has already been mentioned.⁶

Infusion reactions were more likely to occur in indications of head and neck cancer, while other ARs were more likely to occur in indications for colorectal cancer. This is not related to the number of treated patients as, according to the ATIH data, the number of patients treated with cetuximab for head and neck cancer or for colorectal cancer was similar over the period 2009–2010: 4782 patients treated for head and neck cancer vs. 4612 patients treated for colorectal cancer.¹⁷ This association has been shown only once before.⁷

Fatal outcomes in infusion reactions are rare but have already been reported.^{1,2,18–20} In our study, drug-related deaths were all in the infusion reaction group. Even though the indication was not associated with the severity of infusion reactions, drug-related

deaths more often concerned patients with head and neck cancers (5 of 7 deaths). This could be explained by the location of the tumor, which may interfere with intubation, the poor nutritional and general status of these patients, or a lesser response to the corrective treatment of the reaction. Radiotherapy did not seem to be involved as infusion reactions appeared mostly in the first cycle of cetuximab, which is administered before radiotherapy. Tobacco and alcohol may also play a role, as head and neck cancers are associated with tobacco and alcohol consumption.¹⁴ Several studies found a positive association between alcohol consumption and total IgE levels and various allergic reactions, but no clear mechanisms were elucidated.²¹ Patients exposed to tobacco smoke are more likely to have respiratory symptoms as already suggested by O'Neil et al.⁶ The role of tobacco in atopy has not been established, although some studies found a dose-dependent association between exposure to environmental tobacco in the first months of life and IgE sensitization to food allergens.²²

The mechanism of infusion reactions is not clearly understood but an IgE-mediated reaction was demonstrated for the first time by Chung et al. in 2008.⁴ The antigen identified was an oligosaccharide located in the Fab portion of the heavy chain of cetuximab: the galactose- α -1,3-galactose (α 3Gal). These IgE were found in some patients before any contact with cetuximab. This may explain the occurrence of these reactions during the first cycle. Sensitization could occur through food (pork and beef), some parasites, or tick bites.^{4,18} Premedication is actually ineffective in preventing this type of reaction. It is also interesting to note that a French study found a significantly higher prevalence of IgE anti-galactose- α -1,3-galactose in men.¹⁸

This IgE-mediated hypothesis may be reflected by the relative inefficiency of the premedication shown in other studies^{6,7,23} as well as in ours. However, this result in our study should be interpreted with caution given the large amount of missing data. The positive association between severity and first administration could have been related to lighter premedication before the first administration than before subsequent cycles. However, the recommendation of the SPC is bi-premedication (antihistamine and corticosteroid), and in our study, the proportions of patients receiving combination therapy in the first cycle or in all subsequent cycles were no different ($p = 0.682$).

The ability of bi-premedication to reduce the incidence and severity of infusion reactions has been shown in one clinical trial²⁴ (study funded by the maker of Erbitux®) and in the analysis done by the maker of Erbitux® in Europe with pooled data of 2 major trials in colon cancer setting (CRYSTAL and MABEL).¹⁸

This IgE-mediated hypothesis is probably not the only mechanism of infusion reactions seen with cetuximab. Indeed it is surprising not to find more severe reactions beyond cycle 2 (sensitization during first administration). The large proportion of reaction-free reintroductions (55.8%) also goes against the hypothesis of an initial IgE-mediated reaction. There were only a few cases of reintroductions (52 out of 374), which may be explained by the fact that severe reactions led to a definite contraindication to cetuximab.

Another assumption is another mechanism such as an anaphylactoid reaction or another antigen. When reports of cetuximab infusion reactions were compared with other ARs reported with this drug, we found a significant difference for the year of occurrence. Moreover, we noted an increasing tendency since 2007. This raises the question of the new formulation of Erbitux[®] authorized in February 2007.²⁵ Erbitux[®] 2 mg/mL was replaced by Erbitux[®] 5 mg/mL, which contains new additives to reduce aggregates, among them is polysorbate 80. This vehicle has been identified as a cause of immediate reactions with several drugs, including docetaxel²⁶ and omalizumab.²⁷ An anaphylactoid mechanism has been demonstrated with polysorbate 80, without involvement of IgE.²⁸ This new formulation was authorized in January 2007, but it is difficult to date the complete cessation of the old formulation.

This increase may also be a bias linked to increased awareness of this reaction leading to more frequent reporting by health professionals even though such reactions are no more frequent than other reactions. However, there have been no communications from the French or other national authorities on this kind of reaction induced by cetuximab. Nevertheless, the French Health authorities published a warning about other monoclonal antibodies (panitumumab Vectibix[®] in May 2010,²⁹ bevacizumab Avastin[®] in June 2010³⁰). The increased number of reports may also be related to the severity of this kind of reaction, which is a major problem in clinical practice as it leads to early cessation of treatment. The indication could also explain this result as cetuximab was approved for carcinoma of head and neck in 2006.

This study has several limitations. First, the cases retrospectively analyzed in this study consisted of spontaneous reports. This does not allow epidemiological extrapolation to the general population treated with cetuximab. All of the patients considered in our study design are “cases” as they experienced an ADR. Thus only factors associated with the seriousness, or the severity of the reported ADR, rather than their absolute occurrence, could be investigated. Second, the large amount of missing data regarding the background of patients or previous chemotherapy treatment made it impossible to take such factors into account.

In conclusion, analyses of ADR reported with cetuximab to the French Pharmacovigilance database shows that reports of infusion reactions more often concerned patients treated with cetuximab for squamous cell carcinoma of the head and neck than for patients treated for colorectal cancer, that the outcome in these patients was more often fatal and that severe infusion reactions were more likely during the first treatment cycle. Further investigations are needed to assess differences in support care between the two indications. Considering the possibility that these reactions are IgE mediated, reliable tests for their detection need to be readily available. The interest of identifying patients at risk before starting treatment should be investigated. A prospective study may be helpful to identify other risk factors such as medical history and previous chemotherapy. In daily practice, the fatal outcome of these immediate reactions may be prevented by very close monitoring of patients during the first infusion, especially patients with head and neck cancer.

Acknowledgments

The authors acknowledge Dr Côme Lepage and Dr Hervé Watier for the medical contribution, Véronique PIZZOGLIO and Pascal AURICHE from AFSSAPS for the extraction of the French Pharmacovigilance database, and Mr Cédric Collin from AFSSAPS for the ATIH data.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest

None.

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