



Retrospective analysis of premedication, glucocorticosteroids, and H₁-antihistamines for preventing infusion reactions associated with cetuximab treatment of patients with head and neck cancer

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Abstract

Objectives: We evaluated infusion-related reactions associated with cetuximab combination chemotherapy comprising an H₁-receptor antagonist plus dexamethasone as anti-allergy premedications for patients with head and neck cancer.

Methods: We retrospectively evaluated 248 patients who received a cetuximab combination regimen between December 2012 and August 2015. All patients received 5 mg intravenous dichlorpheniramine (H₁-receptor antagonist), and dexamethasone (DEX) was adjusted from 6.6 mg to 13.2 mg according to the emetogenic risk.

Results: We identified 248 subjects, including 13 (5.2%) with infusion-related reactions (grade 1 in five [2.0%], grade 2 in seven [2.8%], and grade 4 in one [0.4%]). The incidence of these reactions in cetuximab combination regimens, each employing an H₁-receptor antagonist, using a higher dose of dexamethasone (13.2 mg) was not significantly lower compared with those using 6.6 mg DEX (2.4% vs 8.3%, respectively; $p = 0.43$). Twelve patients experienced infusion-related reactions

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associated with the first cetuximab administration, and one reaction occurred after the third administration.

Conclusions: The incidence of infusion-related reactions was lower compared with those of previous studies. Dexamethasone combined with an H₁-receptor antagonist was useful for preventing allergic responses. The incidence of infusion-related reactions was not lower with 13.2 mg dexamethasone, and 6.6 mg DEX prevented infusion-related reactions.

Keywords

Cetuximab, infusion reactions, monoclonal antibodies, prophylaxis, head and neck cancer

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Introduction

Cetuximab (Cmab)-induced infusion-related reactions (IRRs) are well-known adverse drug reactions. The acuteness and severity of symptoms associated with Cmab IRRs suggest that they represent type I reactions mediated by pre-existing immunoglobulin (Ig)E antibodies that cross-react with Cmab.¹ IRRs occur in 6%-18% of patients who receive Cmab, and high-grade (Grade 3 and 4) reactions occur in 1%-5%.²⁻⁸ The package insert of Cmab in the United States recommends that anti-allergy prophylactic premedication to treat IRRs caused by Cmab should be restricted to histamine H₁-receptor antagonists (H₁AT), although few studies describe the use of corticosteroids as a premedication. In the MABEL study of colorectal cancer, the incidence of IRRs was higher in patients who received H₁AT alone compared with that of patients who received H₁AT plus a steroid (any grade = 25.6% vs 9.6%; Grade 3/4 = 4.7% vs 1.0%, respectively).⁸ Accordingly, the Japanese Cmab package insert suggests that the use of corticosteroids may reduce the incidence of IRRs, and the administration of dexamethasone (DEX) as an anti-allergy premedication is therefore common in Japan. Few studies report the effects of anti-allergy premedication to prevent Cmab IRRs,^{9,10} although dosage guidance is not available. The staff of the Division of Head and Neck Oncology

of the National Cancer Center Hospital East (NCCHE) decided to use 6.6 mg of DEX with H₁AT. To our knowledge, the effect of H₁AT plus DEX as an anti-allergy premedication for chemotherapy including Cmab for patients with head and neck cancer has not been reported.

Aim of the study

We retrospectively reviewed the effects of the addition of DEX to H₁AT to chemotherapy administered to patients with cancer of the head and neck. Various doses of DEX were used according to the emetogenic risk of the chemotherapy.

Ethics approval

The National Cancer Center Institutional Review Board approved this study (Approval #2014-319). This was a retrospective study, and the requirement for informed consent was waived.

Methods

Subjects and study design

This study was conducted as a retrospective chart review of patients with head and neck cancer who received a Cmab combination regimen, including Cmab alone or Cmab administered with concurrent radiotherapy. Subjects were identified from a

Table 1. Anti-allergy premedication groups and Cmab combination chemotherapy regimens.

Group	Combination	Chemotherapy	H ₁ AT (mg)	DEX (mg)	H ₂ AT (mg)	3-day APR
A	Cmab	RT + Cmab Cmab alone	5	6.6	–	–
B ^c	Cmab + PTX (+CBDCA ^a)	PTX + Cmab CBDCA + PTX + Cmab	5	6.6	20	–
C	Cmab + CBDCA ^b + 5FU	CBDCA + 5FU + Cmab	5	9.9	–	–
D	Cmab + CDDP (+5FU or DOC)	DOC + CDDP + Cmab CDDP + 5FU + Cmab	5	13.2 ^a	–	○

^aThree days of oral aprepitant: 125 mg on day 1, 80 mg on days 2–3

^bCalculated using target AUC = 2

^cOnly Group B was administrated Cmab from 60 to 90 min after premedication because of the administration of other chemotherapy (paclitaxel for 60 min with or without CBDCA for 30 min)

5FU, 5-fluorouracil; APR, aprepitant; CBDCA, carboplatin; CDDP, cisplatin; Cmab, cetuximab; DOC, docetaxel; H₁AT, antihistamine H₁-receptor antagonist (d-chlorpheniramine); H₂AT, antihistamine H₂-receptor antagonist (famotidine); PTX, paclitaxel; RT, radiotherapy.

computer-generated list acquired from the pharmacy database at the NCCHE from December 1, 2012 to August 31, 2015. Cmab (cetuximab, 400 mg/m² and 250 mg/m² as the maintenance and loading doses, respectively) was administered intravenously weekly along with any other chemotherapeutics. Regimens were categorized into Groups A–D according to the combination and doses of DEX, histamine H₂-receptor antagonist (H₂AT), and aprepitant (APR) (Table 1). All patients received d-chlorpheniramine as an H₁AT or famotidine as an H₂AT. Oral APR was administered at 125 mg on day one and at 80 mg on days two and three before cisplatin administration. During the first cycle of Cmab chemotherapy, all subjects received anti-allergy premedication according to the combination of anticancer agents. This regimen was determined using a registered chemotherapy template for head and neck medical oncology included in a computerized provider order-entry system managed by the institution's pharmacy department. Therefore, patients who received the same chemotherapy regimen received the same constitutive anticancer agents, which were calculated according to body surface area,

premedication, and patients' hydration. Only patients in Group B received Cmab 90 min after premedication, because paclitaxel (PTX) was administered first, and Cmab was administered as a component of the second course. After the occurrence of grade 4 IRRs on February 14, 2013, subsequently issued regulations stipulate that a physician must routinely monitor the first and second courses of Cmab for Cmab IRRs, and the majority of the data were therefore considered accurate. The study's endpoint was the incidence of Cmab IRRs in each anti-allergy premedication group (Table 1). Subjects' data were collected from electronic databases. Oncologists evaluated IRRs according to the Common Terminology Criteria for Adverse Events version 4.0.

Data analysis

Bivariate analyses, chi-square tests, or Fisher's exact probability test were used to evaluate the significance of differences among various anti-allergy premedications. All data were analyzed using SPSS version 22.0 (SPSS, Chicago, IL, USA), and $p < 0.05$ was considered statistically significant. The number of patients differed among

Table 2. Patients' characteristics.

Variables		Overall	(%)	IRRs	(%)	No IRRs	(%)
N		248		13	(5.2)	235	(94.8)
Age, years	Median	63		63		63	
	[Range]	[22 – 79]		[35 – 74]		[22 – 79]	
Sex	Male	193	(77.8)	8	(61.5)	185	(78.7)
	Female	55	(22.2)	5	(38.5)	50	(21.3)
Race	Japanese	247	(99.6)	13	(100.0)	234	(99.6)
	Other	1	(0.4)	0		1	(0.4)
Allergy history	Drugs	36	(14.5)	2	(15.4)	34	(14.5)
	Foods	15	(6.0)	0		15	(6.4)
Allergic diseases		11	(4.4)	0		11	(4.7)
Settings	Induction	70	(28.2)	3	(23.1)	67	(28.5)
	Bioradiation	38	(15.3)	3	(23.1)	35	(14.9)
	Palliative	140	(56.5)	7	(53.8)	133	(56.6)
Cmab loading dose, mg	Median	648.5		590		650	
	[Range]	[459–970]		[459–666]		[470–970]	

Cmab, cetuximab; IRRs, infusion-related reactions.

groups because of the study's retrospective design, which reflects daily clinical practice during the study period.

Results

Patients' characteristics and incidence of IRRs

We identified 248 subjects including 13 (5.2%) who experienced IRRs with grade 1 events in five (2.0%), grade 2 events in seven (2.8%), and grade four events in one (0.4%). More than 90% of IRRs ($n=12$) were associated with the first Cmab administration, and one patient experienced IRRs with the third course of Cmab. There were no significant differences between patients with or without IRRs associated with age, Cmab loading dose, history of allergy, or allergic disease (Table 2).

IRRs and premedication

The incidence of IRRs was 8.3% (5/60) in Group A, 5.3% (7/133) in Group B, and 2.4% (1/41) in Group D (Table 3).

The incidence of IRRs in Group D, in which patients received a higher dose of DEX (13.2 mg) and 3 days of APR with H1AT, was not significantly lower compared with that in Group A, in which patients received a lower dose of DEX (6.6 mg) with a H₁AT (2.4% vs 8.3%, $p=0.43$). The incidence of IRRs in Group B was 5.3% (7/133) compared with 8.3% (5/60) in Group A and 2.4% (1/41) in Group D. Severe IRRs (grade 4) were experienced by 0.4% (1/133) of patients in Group B. DEX was not associated with severe adverse reactions.

Discussion

In the present study, 5.2% of patients experienced IRRs, and one patient (0.4%) experienced a severe IRR. These results are comparable with the incidences of Cmab-induced IRRs in patients with head and neck cancer in the EXTREME (12%)¹¹ and in the Bonner (15%) studies.³ However, neither study reported the use of standardized anti-allergy premedication. All patients in the present retrospective study received at least 6.6 mg of DEX and an

Table 3. Incidence of IRRs and premedications.

Group	Combination	N	IRRs	(%)	Gr1	Gr2	Gr3	Gr4
A	Cmab	60	5	(8.3)	1	4	0	0
B ^c	Cmab + PTX (+CBDCA ^a)	133	7	(5.3)	3	3	0	1
C	Cmab + CBDCA ^b + 5FU	14	0		0	0	0	0
D	Cmab + CDDP (+5FU or DOC)	41	1	(2.4)	1	0	0	0

^aCalculated using target AUC = 2

^bCalculated using target AUC = 5

^cOnly Group 2 was administered Cmab 60–90 min after premedication because of the administration of other chemotherapies (paclitaxel for 60 min with or without CBDCA for 30 min)

5FU, 5-fluorouracil; CBDCA, carboplatin; CDDP, cisplatin; Cmab, cetuximab; DOC, docetaxel; PTX, paclitaxel; RT, radiotherapy.

H₁AT before Cmab administration. In the MABEL study, the incidence of IRRs was significantly lower in patients who received an H₁AT and corticosteroids compared with those who received an H₁AT alone.⁸ The package insert for Cmab in Japan suggests that corticosteroid use is beneficial for the prevention of IRRs. Oncologists in Japan generally use DEX as an anti-allergy premedication with an H₁AT, although the benefits are unknown, and suitable doses of DEX are not established. In clinical trials to gain approval of Cmab in Japan, the 053 and 056 studies report incidences of 4% and 6% for Cmab-induced IRRs, respectively.

Oncologists at the NCCHE used DEX at a minimum dose of 6.6 mg as anti-allergy premedication in Phase 2 clinical studies.^{12,13} Accordingly, DEX appears beneficial for decreasing the occurrence of Cmab-induced IRRs. However, our results did not reveal a clear benefit of higher doses of DEX. Although the incidence of IRRs was higher with chemotherapy compared with that of Cmab alone, the numbers of patients in the respective premedication groups were unequal. The package insert of APR states that APR inhibits CYP3A4 and in turn inhibits the metabolism of DEX, a CYP3A4 substrate and that serum levels of DEX double with the use of APR. However, one patient in Group D had a Grade 1 IRR. Numerous patients in Groups A and B, who

received a lower dose of premedication DEX experienced a grade 2 or grade 4 (one case) IRR. This finding suggests that higher doses of DEX may be associated with decreased severity of IRRs, although the differences were not statistically significant.

O'Neil et al.,¹⁴ reported a high incidence of IRRs associated with Cmab in patients treated in Tennessee and North Carolina and evaluated the influence of DEX on Cmab IRRs. The incidence of grade 3 or 4 hypersensitivity reactions was still high (16.7%) when DEX was combined with H₁AT. However, the report did not identify the dose of DEX and did not evaluate the influence of the dose of DEX. Keating, et al.,¹⁵ found that pretreatment with steroids, in addition to diphenhydramine, was associated with a lower risk of experiencing a grade 3 or 4 hypersensitivity reaction. In the present study, all anti-allergy premedication was conducted before Cmab administration, and the incidence of a grade 3 or 4 IRR was <1%. Furthermore, Cmab could be administered first in Cmab-containing regimens to consider the effect of the systemic load of DEX, and the higher dose of DEX was not a significant factor that prevented IRRs. Only patients in Group B were administered Cmab 60–90 min after anti-allergy premedication because of the administration of other chemotherapeutic drugs. The aspects of the chemotherapy regimen

schedule, such as the time lag between DEX and Cmab administration, may result in lower serum levels of DEX at the time the patient received Cmab. Serum levels of DEX are obviously higher immediately after administration compared with those 60–90 min after the administration of the premedication. The incidence of IRRs in Group B was not significantly higher compared with those of the other groups, and the 60- to 90-min time delay did not seem an important influence on the incidence or severity of IRRs.

Previous reports suggest several risk factors for IRRs caused by Cmab.^{1,14–16} Nicole et al. reported head and neck cancer as a risk factor for IRRs (62% vs 29%),¹⁷ although a high incidence of these events was not reported in that study or in Japanese Phase 2 studies.^{12,13} In our study, approximately 10% of patients had a history of allergy, and approximately 5% of patients had allergic disease, although these factors were unrelated to the incidence of IRRs. Atopic disease, tick bites, and allergies to beef or fish eggs are risk factors for IRRs associated with to Cmab,^{14–16} however, the patients in our study did not have these risk factors. The characteristics of our patients varied widely, but our present study or any previous study uncovered evidence indicating that age is a risk factor for IRRs caused by Cmab.

This retrospective study was limited to a specific chemotherapeutic regimen and only included Japanese patients with head and neck cancer. Furthermore, although we included 258 subjects, there were few severe IRRs, which may have limited the power of the analysis to reveal significant differences. Further studies may therefore be required to evaluate the effects of premedication. Another limitation of this study was that we were unable to measure risk factors for IRRs, such as serum IgE levels or other markers of allergy, which are risk factors for severe IRRs. A recent study

found a 100% of negative predictive value for IgE that, which may be relevant.¹⁸ In the present retrospective study, we collected data from patient's records. The subjects were treated in a clinical practice setting, and therefore we did not use tryptase, measured histamine, or performed skin tests when patients experienced IRRs. Therefore, we were unable to identify the mechanism or cause of the IRRs associated with Cmab. The IRRs of the 12 patients were not allergy-dependent episodes, except one patient who had IRRs during the third cycle of Cmab injections. The recommendations of the International Consensus on drug allergy¹⁹ for preventive measures using premedication (e.g. slow injection and pretreatment with steroids and H₁AT) are useful mainly for nonallergic symptoms and may not reliably prevent drug-associated IgE-dependent anaphylaxis.

Conclusion

This is the first study to our knowledge to determine the incidence of IRRs following H₁AT plus DEX used as anti-allergy premedication for Cmab-containing chemotherapy administered to Japanese patients with head and neck cancer. Although the incidence of IRRs was not significantly lower with higher doses of DEX premedication, the incidence was lower compared with those of other studies. DEX premedication, with a minimum dose of 6.6 mg, may prevent IRRs. Cmab could be administered first in Cmab-containing regimens to evaluate the effects of the systemic load of DEX.

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Declaration of conflicting interests

The authors declare that there are no conflicts of interest.

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