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Identifying the Patterns of Adverse Drug Responses of Cetuximab

Ji Hyun Park[1]*

[1]College of Pharmacy, Duksung Women's University, Seoul 01369, Republic of Korea
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ABSTRACT

Background: Monoclonal antibodies for the treatment of patients with different types of cancer, such as cetuximab, have been widely used for the past 10 years in oncology. Although drug information package insert contains some representative adverse events which were observed in the clinical trials for drug approval, the overall adverse event patterns on the real-world cetuximab use were less investigated. Also, there have been no published papers that deal with the full spectrums of adverse drug events of cetuximab using national-wide drug safety surveillance systems. **Methods:** In this study, we detected new adverse event signals of cetuximab in the Korea Adverse Event Reporting System (KAERS) by utilizing proportional reporting ratios, reporting odds ratios, and information components indices. **Results:** The KAERS database included 869,819 spontaneous adverse event reports, among which 2,116 reports contained cetuximab. We compared the labels of cetuximab among the United States, European Union, Australia, Japan, and Korea to compare the current labeling information and newly detected signals of our study. Some of the signals including hyperkeratosis, tenesmus, folliculitis, esophagitis, neuralgia, disseminated intravascular coagulopathy, and skin/throat tightness were not labeled in the five countries. **Conclusion:** We identified new signals that were not known at the time of market approval.

KEYWORDS: Cetuximab, adverse drug event, individual case safety report, pharmacovigilance, signal detection

For the past 10 years, immunotherapy has emerged as a promising approach to combat advanced stages of cancers. The ability of immune system to detect foreign matters and produce proteins (antibodies) against them is one of the essential means by which the body protect itself against diseases. In a similar vein, delivering substantial amount of antibodies targeting the tumor complex has been considered as a potentially effective approach to treat cancer. Monoclonal antibody (mAb) have demonstrated to be a useful addition to the armamentarium for many types of cancer. Pertuzumab, panitumumab, trastuzumab, and cetuximab, mAbs that are directly binding to the receptors of the epidermal growth factor family, result in the diminished function of subsequent signaling pathways.[1)] In addition to signaling interruption, some of these mAbs can also activate antibody-dependent cellular cytotoxicity (ADCC) to cancer cells.[2)]

Cetuximab (Erbitux™), a recombinant human/murine chimeric mAb, binds to the overexpressed epidermal growth factor receptor (EGFR) or human epidermal growth factor receptor1 (HER1). It has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of colorectal cancer and locally advanced squamous cell carcinoma of the head and neck (SCCHN).[3)] Representing 10.2% of the newly diagnosed cancer in the world, colorectal cancer is the second leading cause of death.[4)] SCCHN is the sixth most common cancer, and over 90% of SCCHN of upper gastro-intestinal tract have overexpressed EGFR.[2)] Cetuximab when combined with radiation increased a disease control rate for colorectal cancer by 53%, and improved the median survival time from 29.3 to 49 months.[3,4)] Also, other indicators demonstrated

*Correspondence to: Ji Hyun Park, College of Pharmacy, Duksung Women's University, 33, Samyang-ro 144-gil, Dobong-gu, Seoul 01369, Republic of Korea
Tel: +82-2-901-8703, E-mail: pharmerpark@duksung.ac.kr

favorable results of better life quality for the patients. With respect to side effects, the most commonly reported adverse drug events was rash, within the range of 30% of patients, however, health department has attentively investigated the full spectrums of adverse events in spite of the relatively short usage history of mAbs.[5)]

Toxicities related to mAbs use can be resulted from the intended pharmacological effects of the mAb. For example, mAbs could cause toxicities by interacting with the targeted antigen on the unintended tissue as in the dermatological adverse event cases of cetuximab. Cutaneous toxicities including populopustular rash (acne like rash) or skin dryness are the most common adverse events observed from the use of EGFR inhibitors, however the clear mechanism has not been well explained.[6-9)] Also the non-specific, off-target toxicity can be occurred from the use of mAb, resulting in hypersensitivity which might be driven by the non-human portion of chimeric mAbs.[10)] Other impacting factors, such as producing methods, storage, impurities or cell-line used to manufacture mAbs all contribute to unexpected reactions.[9-11)]

To exploit greater range of unexpected results from the medication use and protect public health, spontaneous adverse event reporting system of Korea (KAERS) was established in 1988. Since then, the Korea Institute of Drug Safety and Risk Management (KIDS) started to monitor adverse drug events observed in the Korean population and make effective policies on the use of medication, which is called pharmacovigilance.[12,13)] KAERS database includes the data collected from spontaneous reports, reports from research (individual case reports, post-marketing surveillance, re-examination, etc), and information from literatures.[13,14)] Korea joined to the World Health Organization (WHO) Program for International Drug Monitoring in 1992, and KAERS database is compatible with the international standard with being ranked in the second most active reporting country following the United States.[15)]

Each document that are collected by the pharmacovigilance database is called individual case safety report (ICSR), which contains the demographic information of patient, administered medications, adverse drug events, and other related information that are required to judge the causality of the medication use and the subsequent adverse events.[16)] Adverse drug event (ADE) means any unwanted incidence during the medication treatment that does not necessarily have a causal relationship. Meanwhile, adverse drug event (ADE) means a harmful or unwanted reaction after the use of medications under normal conditions and is suspected to be associated with the medication use.[17)] Searching for disproportionately represented ADEs and detecting the possible ADEs among them is the main reason to collect ICSRs nation-wide as well as worldwide.[18)] Literally, “all” unexpected events related to the drug use are encouraged to report “spontaneously,” therefore the better approach to understand what ICSR is to see them as a report of ADEs. However, over 90% of ICSRs in Korea are reported by health professionals such as physicians, pharmacists, and nurses who are mandatorily trained how to discriminate ADEs from ADEs, and to report suspicious cases to the pharmacovigilance systems. Owing to the reports from well-trained and alert health professionals, the ICSRs reported in Korea considered to have the highest quality among all nations.[19)]

In spite of the well-established pharmacovigilance systems and the need for understanding the thorough clinical features of cetuximab use, there has been no published articles on the full ADE spectrums of cetuximab. Utilizing ICSR database, the purpose of our study was to demonstrate the patterns of cetuximab ADEs by comparing the number of each reported ADE in cetuximab use with other cancer immunotherapeutic or targeting agents (CITAs), and all other medications, detect signals of cetuximab ADEs from KAERS database, and compare the labels of cetuximab among the 5 major developed countries or continental; United States, European Union, Australia, Japan, and Korea.

Materials and Methods

Data source and Study drug

This study included all spontaneous ICSRs in Korea from January 2013 to December 2017, which collected by Korea Institute of Drug Safety & Risk Management (KIDS). ICSRs includes demographic information on patient, suspected drug information, ADE code, reporter, and causality assessment. The causality assessment was not reflected in this study. Also, the total ICSR numbers of cetuximab are yet fewer as it is a new drug, so we decided not to include the causality assessment results in this analysis. The anonymized spontaneous ICSRs collected by KIDS have been analyzed in this study under the approval of the institutional review board ethics committee of the Korea University with an ethical exemption (IRB-2019-0239).

Generating analytic database, KIDS screened ICSRs without demographic information. Among all the reported drugs, we

identified all the targeted cancer therapy or immunotherapeutic agents that are classified into number 421 by WHO-ATC (World Health Organization-Anatomical Therapeutic Chemical) code drug name.[14,20] ADEs are coded by the Preferred Terms (PT) of WHO-Adverse Reaction Terminology (WHO-ART) for the analysis. The number of reported ADEs were utilized to detect signals of ADEs that could result in a greater number of ICSRs given one patient could have experienced multiple ADEs from the use of medications. We defined unexpected adverse event as the event that is not consistent with applicable product information or characteristics of medication. If an ADE was reported to cause death, life threatening, hospitalization or prolonged hospitalization, or persistent of significant disability, it was defined as a serious ADE.[12,16]

The total number of 869,819 ICSRs were reported between 2013 and 2017 in the KAERS database and ADEs were 3,055,865. Among the ICSRs, the only reports classified as 'suspected' were included. Cetuximab was selected as the study drug and compared with two different groups: all other cancer immunotherapeutic or targeting agents (CITAs) and all other drugs. Also the research publication numbers of each CITA were searched in Pubmed® and Chemotherapy® archives to estimate the current research subjects and volumes of each medication with their generic names.[21,22] Each drug's approval date was also identified through the package insert and Korea Pharmaceutical Information Center database.

Statistical analysis

The descriptive analysis was applied to demonstrate the demographic characteristics of the patients, such as sex and age groups included in the ICSRs. As the next step, a Chi-squared test was utilized to examine the existence of statistically significant difference among different groups by applying $p<0.05$ as the significance level. Signal detection of ADEs was performed by quantitatively measuring disproportionality between an ADE and a drug use. A two-by-two contingency table serves as the framework for the analysis (Table 1).

In our study, we defined a signal that satisfies all three disproportionality indices: proportional reporting ratio (PRR), reporting odds ratio (ROR), and Bayesian confidence propagation neural networks of information component (IC) (Table 1). Using the PRR, a signal is detected if the incidence of the ADE is greater than or equal to three, and the value of PRR is greater than or equal to two. The associated chi-square value is greater than or equal to four. The same standard was applied to ROR. IC identifies a signal if the lower limit of the 95% two-sided confidence interval exceeds 0[23-25] (Table 1). Statistical analysis were performed by STATA 14.0. The detected signals were compared to Erbitux™ labels of the United States, European Union, Australia, Japan, and Korea.

Results

From January 2013 to December 2017, the total of 869,819 ICSRs were collected in KAERS, of which 2,116 included reports on cetuximab use. The total number of 33 CITAs such as sorafenib, rituximab or afatinib were selected to compare the incidence of ADEs to cetuximab (Table 2). Cetuximab was ranked in the fourth place of the most frequently reported medication with ADEs in CITA, with 5,180 adverse reaction reports since it was first put on the market in 2009, per year average ADE reports of 518. The top three most frequently

Table 1. 2×2 contingency table and the related definitions for disproportionality analysis

2×2 contingency table for disproportionality calculation			
	Target drug	All other drugs	Total
Specific drug	A	B	A+B
All other drugs	C	D	C+D
Total	A+C	B+D	A+B+C+D
Definition and signal detection criteria of implemented data mining indices			
Indices	Definition	Criteria of signal detection	
PRR	[A/(A+B)]/[C/(C+D)]	PRR ≥2, Chi-squared ≥4, and A ≥3	
ROR	(A/B)/(C/D)	ROR ≥2, Chi-squared ≥4, and A ≥3	
IC	log[$P(AE, drug)/P(AE)P(drug)$]	Under limit of 95 % confidence interval ≥0	

PRR, proportional reporting ratio; ROR, reporting odds ratio; IC, information component; AE, adverse event

Table 2. Frequency analysis of ADE reports for cancer immunotherapy agents

Drug	Frequency	Top 3 Adverse Events†			Percent	Marketing Year	Per-Year AE Report*
		1	2	3			
sorafenib	20,060	205	1,765	268	28.21	2008	1,824
afatinib	6,417	205	27	327	9.03	2014	1,283
pazopanib	4,755	205	165	268	6.69	2010	528
cetuximab	5,180	27	1	308	7.29	2009	518
rituximab	8,245	572	24	731	11.60	2003	515
nilotinib	3,187	594	27	24	4.48	2010	354
lapatinib	4,054	1,765	205	308	5.70	2007	338
imatinib	3,669	308	27	544	5.16	2006	282
regorafenib	1,556	1,765	716	1,199	2.19	2013	259
trastuzumab	3,378	731	572	570	4.75	2005	241
bevacizumab	2,765	308	572	908	3.89	2007	230
dasatinib	1,817	594	524	725	2.56	2011	227
pertuzumab	986	572	570	205	1.39	2013	164
erlotinib	1,172	27	24	205	1.65	2005	84
sunitinib	839	1,765	165	716	1.18	2006	65
gefitinib	1,009	27	24	205	1.42	2003	63
ramucirumab	248	570	528	24	0.35	2015	62
ceritinib	205	205	268	308	0.29	2015	51
blinatumomab	153	725	1,903	360	0.22	2015	38
nivolumab	136	350	1,141	27	0.19	2015	34
ruxolitinib	185	544	594	566	0.26	2013	31
osimertinib	67	496	1,068	205	0.09	2016	22
crizotinib	166	965	722	1,345	0.23	2011	21
ipilimumab	79	350	716	722	0.11	2014	16
ibrutinib	73	306	314	528	0.10	2014	15
lenvatinib	51	210	205	268	0.07	2015	13
brentuximab vedotin	40	24	1,615	44	0.06	2013	7
vemurafenib	30	27	205	1,361	0.04	2012	4
cobimetinib	8	716	724	27	0.01	2017	4
vandetanib	17	27	425	722	0.02	2013	3
pembrolizumab	7	309	165	572	0.01	2015	2
axitinib	12	481	183	205	0.02	2012	2
daratumumab	3	1,290	528	0	0.00	2017	2
Total	71,102	16,855	14,920	14,200	100.00		

†Top 3 adverse events: the reported number of rash, acne, and nausea respectively which are the most frequently reported ADEs on cetuximab.
*Per-Year AE Reports: the numbers were generated by WHO-UMC Custom Search results.
ADE, adverse drug events; AE, adverse events

Table 3. Trend analysis of ADEs on cancer immunotherapy and targeted-therapeutic agents and the other drugs (number, (%))

Year	Number of ADEs on cetuximab	Number of ADEs on CITA except cetuximab	Number of ADEs on all other drugs
2013	1,985 (38.32)	9,093 (13.79)	524,064 (17.18)
2014	1,317 (25.42)	14,096 (21.38)	564,801 (18.51)
2015	399 (7.70)	13,594 (20.62)	555,630 (18.21)
2016	830 (16.02)	15,816 (23.99)	621,463 (20.37)
2017	649 (12.53)	13,323 (20.21)	784,727 (25.72)
Total	5,180 (100)	65,922 (100)	3,050,685 (100)

ADE, adverse drug event; CITA, cancer immunotherapeutic agent

Table 4. Adverse event reports on cancer immunotherapeutic agents and all other drugs by different characteristics from 2013 to 2017 (number, (%))

Characteristics	Number of ICSRs on cetuximab	Number of ICSRs on all other CITAs	Number of ICSRs on all other drugs	*p*-value
Sex				<0.001
Male	1,409 (66.59)	13,402 (48.17)	347,544 (41.55)	
Female	707 (33.41)	14,423 (51.83)	507,159 (58.45)	
Age group				<0.001
0-19	2 (0.09)	220 (0.79)	53,492 (6.16)	
20-39	101 (4.77)	2,317 (8.33)	139,852 (16.12)	
40-64	1,236 (58.41)	16,566 (59.54)	409,684 (47.21)	
Over 65	777 (36.72)	8,722 (31.35)	264,675 (30.51)	
Reporter				<0.001
Doctor	1,089 (51.91)	15,223 (56.24)	232,143 (26.75)	
Pharmacist	104 (4.96)	1,612 (5.96)	115,178 (13.27)	
Nurse	681 (32.46)	6,737 (24.89)	435,659 (50.21)	
Other health professionals	1 (0.05)	27 (0.10)	1,329 (0.15)	
Consumer	217 (10.34)	3,155 (11.66)	44,611 (5.14)	
Others	6 (0.29)	313 (1.16)	17,081 (1.98)	
NA*	18 (0.85)	758 (2.72)	21,702 (2.50)	
Report center				<0.001
Regional pharmacovigilance center	902 (42.63)	8,894 (31.96)	649,846 (77.37)	
Pharmaceutical company	1,186 (56.05)	18,657 (67.05)	159,712 (19.02)	
Clinic	28 (1.32)	240 (0.86)	20,913 (2.49)	
Pharmacy	0 (0)	33 (0.12)	1,139 (0.14)	
Consumer	0 (0)	0 (0)	6,209 (0.74)	
Others	0 (0)	1 (0.00)	2,052 (0.24)	
NA*	0 (0)	0 (0)	7 (0.00)	
Total	2,116 (100)	27,825 (100)	867,703(100)	

*NA: number of missing reports
ICSR, individual case safety report; CITA, cancer immunotherapeutic agent

reported ADEs of cetuximab were rash, acne, and nausea.

Annual number of ADE reports on cetuximab, CITAs other than cetuximab, and all other drugs was shown in the Table 3. The trend of reported numbers of ADEs on cetuximab use have been decreased until 2015 after which a slight increase was observed for the following years. ADEs on all other medications demonstrated an upward continuous increase. The ADE reports on CITA except cetuximab showed relatively stable values of ADE reports from 2013.

Table 4 shows the characteristics of ICSRs on cetuximab, CITAs without cetuximab, and all other drugs without cetuximab. Compared to all drugs other than cetuximab category, greater number of cases were reported for male among those who were included in the analytic data, and the reports were concentrated on the age group of 40 to 64 or more. Different from the all other drugs category, doctors were the major reporter of ADEs of cetuximab and CITAs. Generally, nurses were the most active reporting professional for other cases. Followed by the regional pharmacovigilance center, pharmaceutical company was the biggest reporting sources.

Table 5 displays the frequently reported ADEs associated with cetuximab usage. Rash was the most frequently reported ADE (474, 9.15%), followed by acne (322, 6.22%) and nausea (295, 5.69%).

Table 5. Frequently reported adverse drug events associated with cetuximab use

Adverse Events	No. of AEs	%
Rash	474	9.15
Acne	322	6.22
Nausea	295	5.69
Pruritus	281	5.42
Diarrhea	214	4.13
Granulocytopenia	201	3.88
Anorexia	182	3.51
Stomatitis	145	2.80
Asthenia	131	2.53
Abdominal pain	118	2.28
Vomiting	115	2.22
Urticaria	112	2.16
Skin disorder	108	2.08
Fever	97	1.87
Constipation	95	1.83
Leucopenia	91	1.76
Dyspnea	88	1.70
Rigors	68	1.31
Mucositis nose	68	1.31
Nail disorder	62	1.20
Others	1,913	36.93
Total	5,180	100

AE, Adverse event

Signals of cetuximab compared with all other CITAs

We detected 34 signals over all other CITAs. Tenesmus (feeling of cramping rectal pain with ineffectual urge to pass stools), lips dry, thirst, onycholysis, seborrhoea, and disseminated intravascular coagulopathy were detected as unexpected signals that were not labeled among the selected five countries. Disseminated intravascular coagulation was a serious and unexpected signal from our disproportionality analysis (Table 6).

Signals of cetuximab compared to all other drugs

We identified 53 signals over all other drugs. Hyperkeratosis, tenesmus, lips dry, respiratory insufficiency, onycholysis, folliculitis, neuralgia, esophagitis, skin tightness, seborrhoea, disseminated intravascular coagulation, and throat tightness were detected as unexpected signals that were not labeled among the selected five countries. Respiratory insufficiency, esophagitis, and disseminated intravascular coagulation were detected as serious, and unexpected ADE signals among the five countries (Table 7).

Discussion/Conclusion

Among the 33 CITAs, cetuximab was ranked top forth both in the total number of reported ADEs and average per year reports. Compared to other agents such as rituximab, trastuzumab, and Bevacizumab that are high ranked on the list of ADEs, studies on cetuximab was less actively performed. Most of the available papers on cetuximab use were focused on the dermatological toxicities, infusion-related reactions, and their management strategies.[6,8,26-35] With regard to the currently available publication results on cetuximab use, this study would be beneficial for the health professionals and immunologists by demonstrating a full range of possible ADEs from the use of cetuximab.

Topical toxicities ranked in top such as rash, acne, and pruritus were the unique constellation of class-specific dermal

Table 6. Detected signals and signal information of cetuximab in the drug labels of 5 countries compared with cancer immunotherapeutic and targeted therapeutic agents by disproportionality analysis

Adverse events description	N	PRR	ROR	IC	Drug labels				
					KR	US	EU	AUS	JP
Acne	322	7.62	8.06	2.36	Y	Y	Y	Y	Y
Skin disorder	108	3.98	4.05	1.71	Y	Y	Y	Y	Y
Mucositis nose	68	3.25	3.28	1.48	Y	Y	Y	Y	Y
Nail disorder	62	6.47	6.53	2.21	Y	Y	Y	Y	Y
Hypotension	49	3.37	3.39	1.52	Y	Y	Y	Y	Y
Anaphylactic reaction	40	21.21	21.37	3.10	Y	Y	Y	Y	Y
Dysphagia	37	9.81	9.87	2.58	Y	N	Y	Y	N
Skin reaction localized	34	2.96	2.98	1.37	Y	Y	Y	Y	Y
Dermatitis	22	3.78	3.80	1.65	Y	Y	Y	Y	Y
Flushing	22	2.39	2.40	1.12	Y	Y	N	N	N
Sputum increased	21	3.47	3.48	1.56	Y	N	N	N	N
Hiccup	17	3.33	3.34	1.51	Y	N	N	N	N
Hypomagnesaemia	15	38.18	38.29	3.36	Y	Y	Y	Y	Y
Tenesmus	14	11.14	11.16	2.68	N	N	N	N	N
Anaphylactic shock	14	35.63	35.73	3.34	Y	Y	Y	Y	Y
Phosphatase alkaline increased	13	3.76	3.77	1.65	N	Y	N	N	N
Allergic reaction	13	5.91	5.92	2.12	Y	Y	Y	Y	Y
Neurologic disorder nose	12	3.92	3.92	1.69	Y	Y	N	N	N
Rash pustular	9	4.24	4.25	1.78	Y	Y	N	N	Y
Lips dry	9	6.74	6.75	2.25	N	N	N	N	N
Thirst	8	5.99	6.00	2.14	N	N	N	N	N
Respiratory insufficiency	8	2.83	2.83	1.32	Y	N	N	Y	Y
Onycholysis	8	5.36	5.37	2.02	N	N	N	N	N
Stupor	6	3.64	3.64	1.61	Y	Y	N	Y	Y
Circulatory failure	5	3.54	3.54	1.58	Y	Y	Y	Y	Y
Purulent discharge	5	5.30	5.31	2.01	Y	Y	N	N	Y
Drug hypersensitivity syndrome	5	3.35	3.35	1.52	Y	Y	Y	Y	Y
Eye pain	4	3.18	3.18	1.46	Y	N	Y	Y	N
Respiratory disorder	4	3.39	3.40	1.53	Y	Y	Y	Y	Y
WBC abnormal nose	4	7.27	7.28	2.32	Y	N	Y	N	N
Seborrhea	3	5.45	5.46	2.04	N	N	N	N	N
Disseminated intravascular coagulation	3	38.18	38.20	3.36	N	N	N	N	N
Tolerance	3	3.82	3.82	1.66	N	N	N	N	N

PRR, proportional reporting ratio; ROR, reporting odds ratio; IC, information component; WBC, white blood cell; KR, Korea; US, the United States; EU, the European Union; AUS, Australia; JP, Japan

Table 7. Detected signals and signal information of cetuximab in the drug labels of 5 countries compared with all other drugs by disproportionality analysis

Adverse events description	N	PRR	ROR	IC	Drug labels				
					KR	US	EU	AUS	JP
Rash	474	2.69	2.86	1.42	Y	Y	Y	Y	Y
Acneiform dermatitis	322	52.79	56.22	5.60	Y	Y	Y	Y	Y
Anorexia	182	2.28	2.33	1.19	Y	Y	Y	Y	Y
Stomatitis	145	5.50	5.63	2.45	Y	Y	Y	Y	Y
Asthenia	131	2.41	2.44	1.26	Y	Y	Y	Y	Y
Skin disorder	108	20.32	20.73	4.30	Y	Y	Y	Y	Y
Leucopenia	91	2.27	2.29	1.18	Y	N	Y	N	N
Rigors	68	3.65	3.68	1.86	Y	Y	Y	Y	N
Mucositis nose	68	6.89	6.97	2.77	Y	Y	Y	Y	Y
Nail disorder	62	11.16	11.28	3.46	Y	Y	Y	Y	Y
Pain	49	2.78	2.80	1.47	Y	Y	Y	Y	Y
Rash erythematous	43	3.31	3.33	1.72	N	Y	N	Y	N
Anaphylactic reaction	40	5.10	5.13	2.34	Y	Y	Y	Y	Y
Dysphagia	37	9.00	9.06	3.15	Y	N	Y	Y	N
Skin reaction localized	34	7.85	7.89	2.96	Y	Y	Y	Y	Y
Paronychia	28	7.78	7.82	2.94	Y	Y	Y	Y	Y
Skin exfoliation	27	4.81	4.83	2.26	Y	Y	Y	Y	Y
Skin dry	23	4.56	4.58	2.18	Y	Y	Y	Y	Y
Dermatitis	22	3.88	3.90	1.95	Y	Y	Y	Y	Y
Flushing	22	2.09	2.09	1.06	Y	Y	N	N	N
Skin discoloration	21	4.01	4.02	2.00	Y	N	N	N	N
Sputum increased	21	2.61	2.61	1.38	Y	N	N	N	N
Hyperkeratosis	19	8.34	8.37	3.04	N	N	N	N	N
Cachexia	18	2.62	2.62	1.39	Y	N	N	N	N
Death	16	3.82	3.83	1.93	Y	Y	Y	Y	Y
Rash maculo-papular	15	4.16	4.17	2.05	N	Y	N	N	N
Hypomagnesaemia	15	5.26	5.27	2.39	Y	Y	Y	Y	Y
Tenesmus	14	8.59	8.61	3.08	N	N	N	N	N
Anaphylactic shock	14	8.16	8.18	3.01	Y	Y	Y	Y	Y
Phosphatase alkaline increased	13	5.31	5.32	2.40	N	Y	Y	N	N
Allergic reaction	13	3.71	3.72	1.89	Y	Y	Y	Y	Y
Neurologic disorder nos.	12	24.98	25.04	4.59	Y	Y	N	N	N
Dysphonia	11	2.22	2.22	1.15	Y	N	N	N	N
Rash pustular	9	8.94	8.95	3.14	Y	Y	N	N	Y
Lips dry	9	6.48	6.49	2.68	N	N	N	N	N
Respiratory insufficiency	8	2.15	2.15	1.10	N	N	N	N	N
Onycholysis	8	33.20	33.24	4.98	N	N	N	N	N
Glossitis	7	4.39	4.39	2.13	Y	Y	Y	Y	Y

Table 7. Continued

Adverse events description	N	PRR	ROR	IC	Drug labels				
					KR	US	EU	AUS	JP
Folliculitis	6	4.02	4.03	2.00	N	N	N	N	N
Neuralgia	5	2.78	2.78	1.47	N	N	N	N	N
Embolism pulmonary	5	2.54	2.54	1.34	Y	Y	Y	Y	Y
Purulent discharge	5	18.69	18.70	4.18	Y	Y	N	N	Y
Esophagitis	4	2.77	2.77	1.46	N	N	N	N	N
Coma hepatic	4	3.43	3.43	1.77	Y	N	N	N	N
LDH increased	4	4.26	4.26	2.08	Y	N	N	N	N
WBC abnormal nos.*	4	37.03	37.05	5.13	Y	Y	Y	N	N
Skin tightness	4	38.20	38.23	5.17	N	N	N	N	N
Seborrhea	3	3.16	3.16	1.66	N	N	N	N	N
Cheilitis	3	3.25	3.25	1.69	Y	Y	Y	Y	Y
Dehydration	3	3.33	3.33	1.73	Y	Y	Y	Y	Y
Disseminated intravascular coagulation	3	5.73	5.73	2.51	N	N	N	N	N
Tolerance	3	45.12	45.15	5.39	N	N	N	N	N
Throat tightness	3	5.42	5.42	2.43	N	N	N	N	N

*nos.: not otherwise specified
PRR, proportional reporting ratio; ROR, reporting odds ratio; IC, information component; LDH, lactate dehydrogenase; WBC, white blood cell; KR, Korea; US, the United States; EU, the European Union; AUS, Australia; JP, Japan

ADEs associated with the original pharmacologic effect of EGFR inhibition.[36] EGFRs are abundantly expressed in the basal layer of epidermis and its appendages, therefore the high incidence of dermatological ADEs induced by EGFR inhibitors are consistent within this class of medications. Compared to profiles of other CITAs or all other medications, the reported cetuximab ADEs were biased to male patients over their female counterparts. Given that one of the main indications for cetuximab is colorectal cancer which is the second frequent cancer around the world with biased incidence in the male population, greater number of reportings for male is not abnormal.[4] Also, the risk of colorectal cancer increases as people gets older, the age related finding of our study makes a complete sense.

Different from the rest of the drug use, ADEs of cetuximab were reported most frequently by doctors. In case of other drugs, nurses are the most active health proffessionals to report ADEs. This might be explained by the severity of the indicated diseases of cetuximab use. Cetuximab is generally indicated for the patients with advanced, metastatic stages or whom with refractory history to other chemotherapies.[3] Most of the patients might be weakend, fragile, and sensitive requiring close monitoring from the physicians. The patient monitoring with cetuximab therapy is usually one of the major concerns of doctors, and the assessment of ADEs after cetuximab might be soley left to the physicians's decision. Nurses were still highly ranked professionals for cetuximab ADE reportings, however, the less intensified than other medications.

We detected 34 signals associated with cetuximab use compared to all other CITAs, and there were 7 unknown signals compared to all other CITAs. According to cetuximab label information suggested by the U.S. FDA, the most common ADEs (incidence ≥25%) are cutaneous adverse reactions including rash, pruritus, and nail changes, headache, diarrhea, and infection.[3] Lips dry, thirst, onlycholysis, and seborrhoea were detected in our study, but not formerly known signals in the package insert of 6 countries. Since dried skin was considered as ADEs from cetuximab use, lips dry could also be presented in the patients. However, specific information on dryness such as dry skin, mouth dryness, or dry eyes were differenciated in all package inserts of 6 countries.[3] It would be better to add specified terms of lips dry for the sake of patients' awareness on the thorough ADE

profile of cetuximab use.[3,20,37] Also nail changes were also included in all label informations in 5 countries, however, onycholisys (nail detach from the skin underneath) was not listed at all.

Acneiform rash was also listed in all 5 labels, however, seborrhoea (excessive sebum) was not included. Possible explanation would be that patients or physicians cannot directly relate the symptom of thirsty and cetuximab use since all other CITAs are not signalling this ADE. Though gestrointestinal side effects are well known after CITA use, input of thirsty in the official labeling of cetuximab is highly recommended for the clearer understanding of clinical profiles of cetuximab use.

In the signal detection of cetuximab over all other drugs, hyperkeratosis, tenesmus, lips dry, respiratory insufficiency, onycholysis, folliculitis, neuralgia, oesophagitis, seborroea, and skin/throat tightness were suggested as unknown ADEs. Tenesmus, which was also identified as a unknown signal in the comparison to other CITAs, was unexpected ADE in both comparisons. It can be associated with several medical conditions such as inflammatory bowel diseases or muscle disorders that affects gut movement.[38] Other gastrointestinal disorders like nausea and diarrhea are well listed in all labels, however, there is no information of possible tenesmus after cetuximab use. Considering that one of the main mechanisms of action of cetuximab brings in mucosal reactions through the body, the reasonable assumption for the incidence of tenesmus would be explained by gastrointestinal mucositis.[32] In the case study by Achermann (2012), two patient were died due to gastrointestinal bleeding after cetuximab use.[39] Further investigation on the incidence of tenesmus in cetuximab use would be beneficial for providing clear epidemiologic and pathophysiologic information.

Respiratory insufficiency was newly detected ADE in this study, which is distinguished from the cardiopulmonary symptoms after cetuximab use. Cardiopulmonary arrest symptoms including circulatory failure or cardiac electrolyte imbalances were detected as signals. Given that the respiratory insufficiency can be resulted from diverse reasons, we encourage further research on this topic in the consequence studies.

Hyperkeratosis is newly detected, unexpected ADE in comparison to all other drugs. Most of the clinical presentations of dermatological toxicities after cetuximab use were acneiform rashes or skin dryness. Hyperkeratosis itself has not been indicated as a possible ADEs after cetuximab use so far. Also neuralgia, which is newly detected unexpected ADE compared to all other drugs, needs to be epidemiologically investigated in future studies.

The incidence of folliculitis and skin or throat tightness could be explained by the expansion of cutaneous tocixities. Oesophagitis can be interpreted as another form of mucositis of body. However, providing the detailed information on these incidences in labels might be more beneficial for the sake of the completeness of clinical information.

DIC was detected in both comparison analysis. It is a life-threatening ADE and the underlying causes of DIC are usually severe tissue injuries, infection, inflammation, or cancer[40]. Considering cetuximab is attacking cancer cells as well as other normal mucosal linings, this could trigger abnormal clotting cascades. Otherwise, exacerbation of cancer might have caused DIC. However, all three disproportionality indices of PRR, ROR, and IC indicate that DIC gained the highest scores compared to other CITAs. DIC was also detected as unknown, unexpected, and serious ADE in comparison to all other drugs, therefore closer investigation on DIC incidence after cetuximab use need to be followed.

Tolerance was detected in both analyses. Since most of immunotherapeutic agents can develop resistance after some period of therapy, it has relatively lower scores in the CITAs comparion[6]. In the comparison with all other drugs that were mostly show far less resistance rate than cetuximab, tolerance showed the second highest scores in all disproportionality analyses. Although tolerance can be an expected result from all cancer therapy, clear comments on the incidence of drug tolerance after cetuximab use might be suggested with labels in the future.

Compared to previous studies, our research is differentiated with respect to the following strong points. Firstly, we utilized KAERS from 2013 to 2017, which covered all incidence of ADEs of all Korean population. There have been no precedent research on the national ADE incidences with cetuximab use. Secondly, our study compared the official labels of 5 representative market places, and detected unknown ADE signals which can brings a unique addition to clinical immunologists in the field of oncology. Also we added potentially serious ADE information that could critically damage public health. Finally, we detected signals of cetuximab use compared with other CITAs, and all other drugs to verify compatibility.

However, our study has some limitations as well. We did

not included causality assessment information of ICSRs, since the major goal of this study was to demonstrate the general patterns of ADEs from the cetuximab use by utilizing cutting edge data-mining skills. Also, most adverse events at institutions still go underreported, though this study covered all incidences from cetuximab use.[41] The whole spectrum of ADEs from cetuximab use could have not been fully uncovered by our study; however, this is the most advanced research to reach the full features of cetuximab ADEs. Also, the fact that the data analyzed in our study limited to the incidences in the Korean population might be a limitation of our study as well. There might be different ADE profiles due to the ethnical diversity of the patients with cetuximab use. Therefore, further pharmacoepidemiologic researches to demonstrate holistic spectrum of ADEs among different ethnicity need to be followed. However, we made big contributions for clinical immunologists in oncology setting, as the early detection of clinically important ADEs is very significant in providing optimized patient centered care.

In conclusion, we identified several new, unknown, and unexpected signals in our study. Among them, hyperkeratosis, tenesmus, and DIC could threaten the safety of the patients using cetuximab.

Conflict of Interest

The author has no conflicts of interest to declare with regards to the contents of this study.

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References

1. Kim JS, Kim YG, Park EJ, *et al.* Cell-based immunotherapy for colorectal cancer with cytokine-induced killer cells. Immune Netw 2016;16(2):99-108.
2. Eric Luedke NB, Julie Roda, Moaz Maqbool Choudhary, *et al.* Cetuximab therapy in head and neck cancer: Immune modulation with interleukin-12 and other natural killer cell-activating cytokines. Surgery 2012;152(3):431-40.
3. Erbitux [package insert]. Eli Lilly and Company; Indianapolis, IN. Available from https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/125084s273lbl.pdf. Accessed September 14, 2019.
4. Gunter M, Alhomoud S, Arnold M, *et al.* Meeting report from the joint IARC-NCI international cancer seminar series: a focus on colorectal cancer. Ann Oncol 2019;30(4):510-9.
5. Mehra R, Cohen RB, Burtness BA. The role of cetuximab for the treatment of squamous cell carcinoma of the head and neck. Clin Adv Hematol Oncol 2008;6(10):742-50.
6. Tamhane UU, Gurm HS. The chimeric monoclonal antibody abciximab: a systematic review of its safety in contemporary practice. Expert Opin Drug Saf 2008;7(6):809-19.
7. Fischer R, Blackmon J, Rajpara A. Cetuximab-induced crusted pustular eruption with patchy alopecia. Dermatol Online J 2014 Oct 15;20(10).
8. Lacouture ME, Anadkat M, Jatoi A, Garawin T, Bohac C, Mitchell E. Dermatologic toxicity occurring during anti-EGFR monoclonal inhibitor therapy in patients with metastatic colorectal cancer: A systematic review. Clinical colorectal cancer 2018 Jun;17(2):85-96.
9. Chularojanamontri L, Tuchinda P, Likitwattananurak C, *et al.* Cutaneous toxicities of epidermal growth factor receptor inhibitors: A prospective study in 60 Asian patients. Asian Pac J Allergy Immunol 2019 Mar;37(1):12-8.
10. Tabrizi MA, Roskos LK. Preclinical and clinical safety of monoclonal antibodies. Drug discovery today 2007;12(13-14):540-7.
11. Weisshaupt C, Budak K, Pestalozzi B. Adverse effects of new oncologic therapies. Praxis (Bern 1994) 2011;100(15):885-91.
12. Singh P, Agrawal M, Hishikar R, Joshi U, Maheshwari B, Halwai A. Adverse drug reactions at adverse drug reaction monitoring center in Raipur: Analysis of spontaneous reports during 1 year. Indian J Pharmacol 2017;49(6):432-7.
13. Choi NK, Park BJ. Adverse drug reaction surveillance system in Korea. J Prev Med Public Health 2007;40(4):278-84.
14. Kim S, Park K, Kim MS, Yang BR, Choi HJ, Park BJ. Data-mining for detecting signals of adverse drug reactions of fluoxetine using the Korea Adverse Event Reporting System (KAERS) database. Psychiatry Res 2017;256:237-42.
15. Lihite RJ, Lahkar M. An update on the pharmacovigilance programme of India. Front pharmacol 2015;6:194.
16. Kim H, Kim N, Lee DH, Kim HS. Analysis of National Pharmacovigilance Data Associated with Statin Use in Korea. Basic Clin Pharmacol Toxicol 2017;121(5):409-13.
17. Schatz S, Weber R. Adverse drug reactions. Pharm Prac 2015;1:5-25.
18. Trippe ZA, Brendani B, Meier C, Lewis D. Identification of substandard medicines via disproportionality analysis of individual case safety reports. Drug safety 2017;40(4):293-303.
19. Anonymous. VigiBase now contains around 17 million ADR reports. Reactions Weekly. 2018;1700(1):3.
20. Korea Pharmaceutical Information Center. Targeted cancer therapy and cetuximab. 2019. Available from http://www.health.kr/Menu.PharmReview/View.asp?PharmReview_IDX=8373. Accessed September 14, 2019.
21. Korean Association of Immunologists. Immune Network. Available from https://immunenetwork.org/. Accessed September 14, 2019.
22. NLM Technical Bulletin. Free web-based access to NLM databases. Available from https://www.nlm.nih.gov/pubs/techbull/mj97/mj97_web.html. Accessed September 15, 2019.
23. Bate A, Lindquist M, Edwards IR, *et al.* A Bayesian neural network method for adverse drug reaction signal generation. Eur J Clin Pharmacol;54(4):315-21.
24. Bate A, Evans SJW. Quantitative signal detection using spontaneous ADR reporting. Pharmacoepidemiol Drug Saf 2009;18(6):427-36.

25. Bate A, Hornbuckle K, Juhaeri J, et al. Hypothesis-free signal detection in healthcare databases: finding its value for pharmacovigilance. Ther Adv Drug Saf 2019;10:2042098619864744.
26. Gerber PA, Buhren BA, Kurle S, et al. Therapy with epidermal growth factor receptor inhibitors. Clinical spectrum of cutaneous adverse effects. Hautarzt 2010;61(8):654-61.
27. Tomková H, Kohoutek M, Zábojníková M, Pospísková M, Ostrízková L, Gharibyar M. Cetuximab-induced cutaneous toxicity. J Eur Acad Dermatol Venereol. 2010;24(6):692-6.
28. Soussan-Dahan M, Lapeyre-Mestre M, Bondon-Guitton E, Delord JP, Despas F. Cetuximab cutaneous adverse drug reactions: a marker of efficacy for metastatic colorectal cancer and head-neck cancer? Therapie 2014;69(6):499-507.
29. Macdonald JB, Macdonald B, Golitz LE, LoRusso P, Sekulic A. Cutaneous adverse effects of targeted therapies: Part I: Inhibitors of the cellular membrane. J Am Acad Dermatol 2015;72(2):203-18.
30. Štulhofer Buzina D, Martinac I, Ledić Drvar D, Čeović R, Bilić I, Marinović B. Adverse reaction to cetuximab, an epidermal growth factor receptor inhibitor. Acta Dermatovenerol Croat 2016;24(1):70-2.
31. Cho YT, Chen KL, Sheen YS, *et al.* Purpuric drug eruptions caused by epidermal growth factor receptor inhibitors for non-small cell lung cancer: A clinicopathologic study of 32 cases. JAMA dermatol 2017;153(9):906-10.
32. Aw DC, Tan EH, Chin TM, Lim HL, Lee HY, Soo RA. Management of epidermal growth factor receptor tyrosine kinase inhibitor-related cutaneous and gastrointestinal toxicities. Asia Pac J Clin Oncol 2018;14(1):23-31.
33. Annunziata MC, Ferrillo M, Cinelli E, Panariello L, Rocco D, Fabbrocini G. Retrospective analysis of skin toxicity in patients under anti-EGFR tyrosine kinase inhibitors: Our experience in lung cancer. Open Access Maced J Med Sci 2019;7(6):973-7.
34. Chan L, Cook DK. A 10-year retrospective cohort study of the management of toxic epidermal necrolysis and Stevens-Johnson syndrome in a New South Wales state referral hospital from 2006 to 2016. Int J Dermatol 2019;58(10):1141-7.
35. Yalici-Armagan B, Ayanoglu BT, Demirdag HG. Targeted tumour therapy induced papulopustular rash and other dermatologic side effects: a retrospective study. Cutan Ocul Toxicol 2019;38(3):261-6.
36. Shah RR, Shah DR. Safety and tolerability of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors in oncology. Drug Saf 2019;42(2):181-98.
37. Bou-Assaly W, Mukherji S. Cetuximab (erbitux). AJNR Am J Neuroradiol 2010;31(4):626-7.
38. Womack N, Williams N, Holmfield J, Morrison J. Pressure and prolapse--the cause of solitary rectal ulceration. Gut 1987;28(10):1228-33.
39. Achermann Y, Frauenfelder T, Obrist S, Zaugg K, Corti N, Günthard HF. A rare but severe pulmonary side effect of cetuximab in two patients. BMJ Case Rep 2012;2012:bcr0320125973.
40. Levi M, Ten Cate H. Disseminated intravascular coagulation. N Engl J Med 1999;341(8):586-92.
41. Shaw G. Most adverse events at hospitals still go unreported. Available from https://www.the-hospitalist.org/hospitalist/article/125141/most-adverse-events-hospitals-still-go-unreported. Accessed September 14, 2019.

Author's information
Ji Hyun Park, Professor