Dermatol Ther (Heidelb) (2022) 12:1041–1054
https://doi.org/10.1007/s13555-022-00712-2

ORIGINAL RESEARCH

Drug Utilization and Medical Cost Study Focusing on Moisturizers in Cancer Patients Treated with Molecular Targeted Therapy: A Retrospective Observational Study Using Data from a Japanese Claims Database

Yoshio Kiyohara · Toshiya Matsuzaki · Lida Teng · Momoyo Kishida · Akira Kanakubo · Anastasiia Motrunich · Yoshie Onishi · Ataru Igarashi

Received: December 9, 2021 / Accepted: March 12, 2022 / Published online: April 10, 2022

ABSTRACT

Introduction: Molecular targeted therapies (MTTs) cause skin disorders in patients with cancer, and moisturizers are useful treatments; however, their actual use and costs are unknown. Our purpose was to examine the use and costs of moisturizers prescribed for xerosis (asteatosis) in patients with cancer treated with MTTs.

Methods: We used data from a Japanese hospital-based claims database. The index date was the first date of MTT prescription from October 2011 to April 2018 (selection period), and the follow-up period was 1 year from the index date. Patients treated with MTTs during the selection period and who were not prescribed moisturizers in the 6 months before the index date were included as the study cohort. Timing, duration, amount, and costs of the prescribed moisturizers and total medical costs were analyzed.

Results: Among the 78,190 patients in the study cohort, 27,906 patients (35.7%) were prescribed moisturizers during follow-up. Moisturizer prescription timing, duration, and volume were inconsistent. The average annual total medical costs for treating patients with MTT who were prescribed moisturizers was JPY 6.165 million (USD 53,797) per patient, and the moisturizer costs were JPY 6033 (USD 53). The number of patients who used moisturizers showed an increasing trend.

Conclusion: No consistent patterns were observed for the timing or duration of moisturizer use, which suggests various developmental patterns of skin disorders. Furthermore, medical costs for moisturizers accounted for only a small proportion of the total medical costs required for cancer treatment.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13555-022-00712-2.

Y. Kiyohara
Dermatology Division, Shizuoka Cancer Center, Shizuoka, Japan

T. Matsuzaki · L. Teng · A. Igarashi
Department of Health Economics and Outcomes Research, Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, Japan

M. Kishida · A. Kanakubo (✉)
Medical Affairs Department, Maruho Co., Ltd., 1-11-1, Nakatsu, Kita-ku, Osaka 531-0071, Japan
e-mail: kanakubo_dss@mii.maruho.co.jp

A. Motrunich
Creativ-Ceutical, Rotterdam, The Netherlands

Y. Onishi
Creativ-Ceutical K.K., Tokyo, Japan

A. Igarashi
Unit of Public Health and Preventive Medicine, Yokohama City University School of Medicine, Kanagawa, Japan

Keywords: Molecular targeted therapy; Dry skin; Heparinoid; Moisturizer; Medical cost; Claims data analysis

Key Summary Points
Why carry out this study?
Moisturizers are used for skin disorders caused as an adverse reaction of molecular targeted therapies in patients with cancer.
Cost and use of moisturizers are not clear in clinical practice.
This study was to analyze the use and costs of moisturizers in patients treated with molecular targeted therapies, using a health insurance claims database.
What was learned from the study?
Moisturizer prescription timing, duration, and volume were inconsistent.
The moisturizer costs were only a small proportion of the total medical costs required for cancer treatment, and use of moisturizers may contribute to continuation of molecular targeted therapy (MTT) treatment.

INTRODUCTION

Among anticancer drugs, molecular targeted therapies (MTTs), particularly epidermal growth factor receptor (EGFR) inhibitors, multikinase inhibitors, and BCR-ABL tyrosine kinase inhibitors, may cause skin disorders as an adverse reaction. Patients may develop hand–foot syndrome (HFS), xerosis (asteatosis), and acneiform folliculitis, and moisturizers are used as treatments [1]. Clinical practice guidance in Japan [2] evaluates the topical application of moisturizers for HFS, xerosis, and acneiform folliculitis caused by treatment with MTTs. Topical application of moisturizers is a grade B recommendation (recommendable with evidence) for HFS and is considered "useful and recommended." The recommendation grade for xerosis is C1a (can be used, but, because of insufficient scientific evidence, is less recommendable than therapies with evidence), and "the use of moisturizers taking advantage of their characteristics is recommended in order to improve dermatitis and subjective symptoms." The recommendation grade for acneiform folliculitis is C1b (no evidence, but the use is not denied), and the guidance states that "the topical application of moisturizers may be considered." Case series describing the clinical usefulness of topical agents in patients being treated with MTTs have been reported [3, 4]; however, there are no controlled studies.

The usefulness of heparinoids, petrolatum, and urea, which are used as prescription moisturizers in Japan, has been reported for the treatment of both primary xerosis and xerosis caused by other diseases, drugs, and therapies; for example, dryness due to MTT treatment [4], radiation dermatitis associated with radiotherapy in patients with breast cancer [5, 6], and dryness and pruritus in patients on dialysis [7]. Prescribed moisturizers contribute to adherence to topical therapy because physicians, nurses, and pharmacists explain directly to the patients the necessity of moisturizers and how to apply them. Treatment of xerosis caused by cancer treatment tends to be neglected relative to the treatment of the underlying disease. However, the therapeutic effect of EGFR inhibitors is higher in patients who develop skin disorders [8, 9]. Therefore, the treatment of skin disorders conceivably contributes to the continuation of treatment with MTT. However, the current status of moisturizer use is unclear.

The purpose of this study was to analyze the utilization patterns and medical costs of moisturizers in patients treated with MTT, using a health insurance claims database.

METHODS

This was a retrospective observational study using a commercial Medical Data Vision (MDV) database of secondary, unlinkable anonymized data; institutional review board approval was not required.

Data Source

We used the Japanese hospital-based claims database developed by Medical Data Vision Co., Ltd. (Tokyo, Japan) for our analyses. The MDV database comprises approximately 28 million patients from 400 hospitals in Japan that use the diagnosis-related-group-like fixed payment system, which is called the Diagnosis Procedure Combination (DPC) system in Japan. These hospitals account for 22% of all acute-phase hospitals and are widely distributed throughout Japan. The MDV database uses an anonymized patient identifier and stores the following patient information: sex, birth year, date of medical service, diagnosis codes, hospitalization, medical procedures, test orders, operations, and prescriptions.

The source cohort in this study comprised patients who were prescribed any MTT (Online Resource 1) between April 2008 and April 2019 (n = 190,536) with continuous enrollment for at least 12 months.

The patient selection period was from October 2011 to April 2018. The follow-up period was 1 year from the index date, which was defined as the first prescription date of MTT, and the pre-index period was defined as the 6-month period before the index date. To investigate the use of moisturizers after completion of treatment with MTT, we defined the "washout period" (end of MTT treatment) as 56 days after the last use of MTT. The study cohort was determined by evaluating patients according to the inclusion and exclusion criteria.

Inclusion criteria:

Patients who were treated with the MTTs listed in Supplementary Table S1 during the patient selection period.

Exclusion criteria:

Patients to whom any of the following conditions applied:

- not treated with the defined MTTs during the patient selection period;
- prescribed at least one moisturizer (heparinoids, petrolatum, urea) within the pre-index period;
- prescribed at least one MTT within the pre-index period;
- not continuously observed in the database during the follow-up period (patients must have had at least one medical claim each quarter within the follow-up period);
- age < 18 years at the index date; and
- prescribed MTT drugs from more than one MTT category at the index date.

Patient Characteristics

The following patient characteristics data were collected:

- age at the index date;
- sex;
- cancer type (International Classification of Diseases version 10 (ICD-10) codes: C00–C96);
- type of MTT being used; and
- type of moisturizer [Anatomical, Therapeutic, Chemical Classification (ATC) codes: C05B0 (heparinoid), V07A0 (petrolatum), and D02A0 (urea)].

Statistical Analysis

The following variables describing the use of moisturizers were analyzed using descriptive statistics:

- number of days for which a patient was treated with MTT during the follow-up period;
- total number of days for which a patient used moisturizers during the follow-up period, total amount (g) of prescribed moisturizers, and the number and proportion of patients who were prescribed moisturizers (by month);
- total number of days for which a patient used moisturizers after the washout period, total amount (g) of prescribed moisturizers, and the number and proportion of patients who were prescribed moisturizers during the follow-up period;
- whether treatment with radiotherapy was performed during the follow-up period

(according to the presence of the management/implementation fee for radiotherapy, M001) and, if so, the number of days a patient received treatment; and
- total medical costs 6 months and 12 months from the index date, and costs of outpatient visits, hospitalization, prescribed drugs, and radiotherapy (exchange rate of USD 1 = JPY 114.59 as of April 2019).

Descriptive analyses were performed using standard descriptive statistics. For continuous variables, sample sizes (*n*), measures of central tendency (mean, median), and measures of variation (standard deviation, minimum, maximum, quartiles, and/or percentiles) are provided. For categorical variables, frequency tables containing sample sizes and proportions (%) for the different categories are presented. We also performed analyses stratified by heparinoids, petrolatum, and urea. All analyses were performed using SAS software version 9.3 (SAS Institute, Cary, NC, USA). Note that the number of prescription days for moisturizers was set at 28 days for each moisturizer prescription. If there were multiple prescriptions, and the interval between prescription dates was less than 28 days, the number of prescription days for the moisturizer was set to the number of days between prescription dates.

RESULTS

Of 190,536 patients in the source cohort, 78,190 patients were included in the study cohort. Among the study cohort, 27,906 patients (35.7%) were prescribed moisturizers (Group M) and 50,284 patients (64.3%) were not prescribed moisturizers (Group N) (Fig. 1).

Patient Demographics

Table 1 presents the patients' background characteristics, groups according to the use of moisturizers, and groups divided by the type of moisturizer (heparinoids, petrolatum, urea, and a combination of two or more moisturizers). When Group N (50,284 patients) was compared with Group M (27,906 patients), the proportion of men was slightly higher versus women (47.4% vs. 45.4%, respectively), and the mean age was also slightly higher (65.7 years versus 64.7 years, respectively) in Group M. Also in Group M, users of heparinoids accounted for 72.6% (n = 20,265) of the patients, petrolatum 14.2% (n = 3960), urea 10.6% (n = 2952), and a combination of moisturizers 2.6% (n = 729). Among the MTT groups with ≥ 1000 patients, the proportion of moisturizer users was highest in the EGFR inhibitor group (71.4%), followed by the multikinase inhibitor group (50.2%), and the immune checkpoint inhibitor group (42.1%), and lowest in the Janus kinase (JAK) inhibitor group (10.7%), BCR-ABL inhibitor group (15.4%), and anti-cluster of differentiation 20 (CD20) antibody group (23.2%) (Table 2).

Among 78,190 patients who were treated with MTT, the most common cancer codes were C81–96 "malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissue" (34.7%), when codes C76–80 "malignant neoplasms of ill-defined, secondary and unspecified sites" were excluded (Supplementary Table S2). Moreover, when the types of cancer with ≥ 1000 patients (eight types) were compared, the proportion of moisturizer users in MTT group was high in patients with respiratory system (47.9%), digestive system (45.7%), or urinary system (45.6%) cancer and low in patients with breast (32.2%), female genital (27.2%), or lymphoid tissue (24.1%) cancer.

Moisturizer Use

Number of Days Patients Were Treated with Anticancer Drugs (MTTs) during the Follow-Up Period

Regarding the number of days patients were treated with MTTs during the follow-up period, data were collected according to MTT category and were further divided into an oral drug group and an injectable drug group (Supplementary Table S3). In the EGFR inhibitor group, one of the groups in which the proportion of moisturizer users was the highest, moisturizer users had more treatment days for both oral

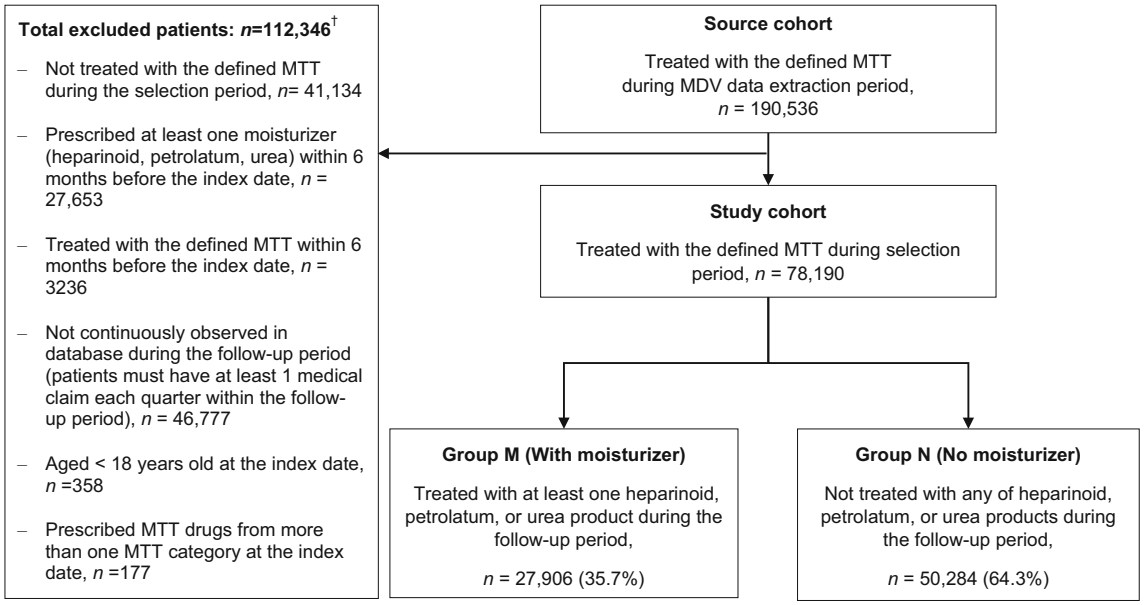

Fig. 1 Study flowchart. †Patients were excluded for several reasons; therefore, the sum of the excluded patients is greater than the total number of excluded patients. *MTT* molecular targeted therapy. Data extraction period: April 2008 to April 2019. Index date: date of the first MTT prescription. Selection period: October 2011 to April 2018. Follow-up period: 1 year from the index date

drugs (252.1 ± 106.4 versus 225.5 ± 120.3, mean ± SD) and injectable drugs (11.9 ± 9.7 versus 9.0 ± 8.8, mean ± SD) compared with patients who did not use moisturizers. In both Group M and Group N, many anticancer drugs were prescribed for a different number of days. However, no consistent pattern was observed in the prescription length.

Total Number of Days for Which a Patient Used Moisturizers during the Follow-up Period, Total Amount (g) of Prescribed Moisturizers, and the Number and Proportion of Patients Who Were Prescribed Moisturizers by Month

The prescription length in days and the amount of moisturizers prescribed during the follow-up period are presented in Table 3. The mean amount of heparinoids (22,537 patients) administered was 393.6 g (median 150 g, Q1–Q3 60–430 g), and the mean prescription length was 92.2 days (median 56 days, Q1–Q3 28–127 days). The mean amount of petrolatum (6615 patients) administered was 127.8 g (median 50 g, Q1–Q3 20–100 g), and the mean prescription length was 48.5 days (median 28 days, Q1–Q3 28–56 days). The mean amount of urea formulations (4356 patients) administered was 174.4 g (median 80 g, Q1–Q3 40–200 g), and the mean prescription length was 70.3 days (median 47 days, Q1–Q3 28–84 days).

For patients who were prescribed moisturizers, the timing of the start of the moisturizer prescription after the MTT prescription date and the number of patients who were prescribed moisturizers at each timepoint are shown in Supplementary Fig. S1. Moisturizers were prescribed for 31.5% of the patients within 1 month from the start of MTT prescriptions, for 74.0% within 6 months and 100% within 12 months. According to the inclusion criteria, patients whose prescriptions were started after the 12th month were not included in the study cohort.

Table 1 Baseline characteristics (at the index date) for the patient cohort

	Overall		All (no moisturizer)		All (with moisturizer)		Heparinoid		Petrolatum		Urea		Combination	
	78,190		50,284	64.3%	27,906	35.7%	20,265	72.6%	3960	14.2%	2,952	10.6%	729	2.6%
Sex, *n* (%)														
Male	36,041	46.1%	22,805	45.4%	13,236	47.4%	9588	47.3%	1841	46.5%	1481	50.2%	326	44.7%
Female	42,149	53.9%	27,479	54.7%	14,670	52.6%	10,677	52.7%	2119	53.5%	1471	49.8%	403	55.3%
Age														
Mean (SD)	65.07 (12.25)		64.71 (12.50)		65.73 (11.76)		65.57 (11.67)		66.15 (12.34)		66.41 (11.47)		65.13 (12.05)	
95% CI	64.99–65.16		64.60–64.82		65.59–65.87		65.41–65.73		65.77–66.54		65.99–66.82		64.26–66.01	
Min, Max	18, 99		18, 98		18, 99		18, 97		18, 99		18, 94		18, 90	
Median	67		66		67		67		68		68		66	
Age category (years), *n* (%)														
18–34	1358	1.7%	980	2.0%	378	1.4%	255	1.3%	78	2.0%	30	1.0%	15	2.1%
35–44	3970	5.1%	2726	5.4%	1244	4.5%	923	4.6%	168	4.2%	115	3.9%	38	5.2%
45–54	9099	11.6%	6102	12.1%	2997	10.7%	2212	10.9%	416	10.5%	302	10.2%	67	9.2%
55–64	18,552	23.7%	12,023	23.9%	6529	23.4%	4778	23.6%	866	21.9%	691	23.4%	194	26.6%
65–74	27,301	34.9%	17,144	34.1%	10,157	36.4%	7483	36.9%	1375	34.7%	1049	35.5%	250	34.3%
75–	17,910	22.9%	11,309	22.5%	6601	23.7%	4614	22.8%	1057	26.7%	765	25.9%	165	22.6%

SD standard deviation, *CI* confidence interval

Table 2 Number of patients and the proportion of moisturizer users by MTT group

	Overall	All (no moisturizer)		All (with moisturizer)		Details of moisturizer							
						Heparinoid		Petrolatum		Urea		Combination	
MTT group (at the index date), *n* (% of usage in the MTT group)													
VEGF inhibitor	19,728	11,804	59.8%	7924	40.2%	6060	30.7%	869	4.4%	782	4.0%	213	1.1%
Anti-CD20 antibody	17,568	13,492	76.8%	4076	23.2%	2465	14.0%	1087	6.2%	449	2.6%	75	0.4%
HER2 inhibitor	12,026	8099	67.3%	3927	32.7%	3000	24.9%	440	3.7%	389	3.2%	98	0.8%
EGFR inhibitor	7177	2056	28.6%	5121	71.4%	4180	58.2%	373	5.2%	391	5.4%	177	2.5%
BCR-ABL inhibitor	6387	5406	84.6%	981	15.4%	668	10.5%	185	2.9%	112	1.8%	16	0.3%
Proteasome inhibitors	4031	2715	67.4%	1316	32.6%	757	18.8%	358	8.9%	177	4.4%	24	0.6%
Immune checkpoint inhibitor	2699	1564	57.9%	1135	42.1%	918	34.0%	153	5.7%	47	1.7%	17	0.6%
Multikinase inhibitor	2501	1246	49.8%	1255	50.2%	744	29.7%	106	4.2%	342	13.7%	63	2.5%
VEGFR inhibitor	2067	1242	60.1%	825	39.9%	603	29.2%	91	4.4%	113	5.5%	18	0.9%
mTOR inhibitor	1186	732	61.7%	454	38.3%	313	26.4%	54	4.6%	79	6.7%	8	0.7%
ALK inhibitor	774	614	79.3%	160	20.7%	129	16.7%	18	2.3%	9	1.2%	4	0.5%
Retinoid	561	300	53.5%	261	46.5%	114	20.3%	116	20.7%	26	4.6%	5	0.9%
JAK inhibitor	457	408	89.3%	49	10.7%	35	7.7%	13	2.8%	1	0.2%	0	0.0%
Antibody–drug conjugate (ADC)	380	244	64.2%	136	35.8%	94	24.7%	26	6.8%	9	2.4%	7	1.8%
CDK 4/6 inhibitor	299	203	67.9%	96	32.1%	66	22.1%	21	7.0%	7	2.3%	2	0.7%
Anti-CCR4 antibody	215	54	25.1%	161	74.9%	98	45.6%	44	20.5%	18	8.4%	1	0.5%
Anti-SLAMF7 antibody	55	44	80.0%	11	20.0%	9	16.4%	2	3.6%	0	0.0%	0	0.0%
BTK inhibitor	49	40	81.6%	9	18.4%	7	14.3%	0	0.0%	1	2.0%	1	2.0%
Anti-CD38 antibody	15	13	86.7%	2	13.3%	2	13.3%	0	0.0%	0	0.0%	0	0.0%
Histone deacetylase inhibitors	11	5	45.5%	6	54.5%	3	27.3%	3	27.3%	0	0.0%	0	0.0%
Anti-CD52 antibody	3	2	66.7%	1	33.3%	0	0.0%	1	33.3%	0	0.0%	0	0.0%
BRAF inhibitor	1	1	100.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%

Table 2 continued

	Overall	All (no moisturizer)		All (with moisturizer)		Details of moisturizer							
						Heparinoid		Petrolatum		Urea		Combination	
Bispecific CD19-directed CD3 T-cell engager antibody construct	0	0	–	0	–	0	–	0	–	0	–	0	–
FLT3-AXL inhibitor	0	0	–	0	–	0	–	0	–	0	–	0	–
MEK inhibitor	0	0	–	0	–	0	–	0	–	0	–	0	–
PARP inhibitor	0	0	–	0	–	0	–	0	–	0	–	0	–
Radioisotope-labeled antibody	0	0	–	0	–	0	–	0	–	0	–	0	–

EGFR epidermal growth factor receptor, *HER2* human epidermal growth factor receptor, *mTOR* mammalian target of rapamycin, *VEGF* vascular endothelial growth factor, *VEGFR* VEGF receptor, *CD* cluster of differentiation, *CCR4* CC chemokine receptor 4, *SLAMF7* signaling lymphocytic activation molecule F7, *BCR-ABL* BCR-ABL oncogene, *FLT3-AXL* FMS-like tyrosine kinase 3/receptor tyrosine kinase AXL, *ALK* anaplastic lymphoma kinase, *BTK* Bruton's tyrosine kinase, *JAK* Janus kinase, *BRAF* B-raf oncogene, *MEK* mitogen-activated extracellular signal-regulated kinase, *CDK 4/6* cyclin-dependent kinases 4/6, *PARP* poly (ADP-ribose) polymerase

Table 3 Proportion of patients, quantity, and prescription days of heparinoids/petrolatum/urea in all patients receiving moisturizers

	n (%)		Quantity (g)		Period (days)	
			Mean (SD)	Median (Q1–Q3)	Mean (SD)	Median (Q1–Q3)
Heparinoids	22,537	80.8%	393.6 (692.8)	150 (60–430)	92.2 (79.4)	56 (28–127)
Petrolatum	6615	23.7%	127.8 (304.5)	50 (20–100)	48.5 (42.3)	28 (28–56)
Urea	4356	15.6%	174.4 (293.5)	80 (40–200)	70.3 (64.4)	47 (28–84)

n number, *SD* standard deviation, *Q1–Q3* first to third quartile

% indicates the percentage of the total number of patients receiving moisturizers calculated cumulatively from the index date up to the end of follow-up

Total Number of Days for Which a Patient Used Moisturizers after the Washout Period and the Total Amount (g) of Prescribed Moisturizers

The prescribed amount of each moisturizer and the prescription length in days after the washout period were calculated as during the follow-up period. The mean amount of heparinoids (3932 patients) administered was 213.5 g (median 100 g, Q1–Q3 50–250 g), and the mean prescription length was 53.1 days (median 31 days, Q1–Q3 28–67 days). The mean amount of petrolatum (1335 patients) administered was 135.5 g (median 50 g, Q1–Q3 20–100 g), and the mean prescription length was 39.4 days (median 28 days, Q1–Q3 28–43 days). The mean amount of urea formulations (657 patients) administered was 121.9 g (median 60 g, Q1–Q3 40–120 g), and the mean prescription length was 47.4 days (median 28 days, Q1–Q3 28–56 days).

Treatment with Radiotherapy during the Follow-up Period (Medical Remuneration Points and Management/ Implementation Fee for Radiotherapy, Code: M001)

The number of patients treated with radiotherapy during the follow-up period and the number of days for which patients received treatment are presented in Supplementary Table S4. In the study cohort, 10.0% of the patients (7801 patients) received concomitant radiotherapy, and the mean length of treatment was 22.8 days (median 20 days, Q1–Q3 15–-26 days). The proportion of moisturizer users was higher in patients who received radiotherapy than in those who did not receive radiotherapy.

Total Medical Costs 6 Months and 12 Months from the Index Date, and the Costs of Outpatient Visits, Hospitalization, Drugs (MTTs, Other Drugs, and Moisturizers), and Radiotherapy

When the total medical costs of cancer treatment were calculated by item over the 6-month and 12-month periods after the index date, medical costs for Group M were higher than for Group N by USD 4078 (USD 32,866 versus 28,788; JPY 0.467 million, 3.766 million versus 3.299 million) at 6 months and USD 8983 (USD 53,797 versus 44,814; JPY 1.029 million, 6.165 million versus 5.135 million) at 12 months (Table 4; USD, Supplementary Table S5; JPY). In Group M, the moisturizer cost was USD 35 ± 65 (JPY 4008 ± 7453, mean ± SD) at 6 months and USD 53 ± 108 (JPY 6033 ± 12,344, mean ± SD) at 12 months, which accounted for approximately 0.1% of the total medical costs. The moisturizer costs accounted for 0.86% of the difference between the two groups at 6 months and 0.59% at 12 months.

We observed an increasing trend in both the proportion of moisturizer users and the amount of moisturizer used per patient over time (Supplementary Table S6).

Overall, changes in the proportion of moisturizer users over time in the MTT groups with ≥ 1000 patients showed a continuous year-to-year increase (Supplementary Fig. S2).

DISCUSSION

Nationwide Estimation of the Number of Patients Receiving MTT

As of 2019, the MDV database covered 22% of acute-phase medical institutions in the DPC system in Japan. Provided that all patients with cancer are seen at acute-phase medical institutions, we estimate that approximately 870,000 cancer patients were treated with MTT during the follow-up period in this study [the number of patients included as the source cohort (190,536) divided by 0.22]. The Ministry of Health, Labour, and Welfare in Japan estimated that, as of 2017, there were 1,782,000 patients with cancer. Considering that most anticancer drugs developed since 2000 are MTTs, "patients treated with MTT" who were included in our study cohort are expected to account for a large proportion of patients with cancer.

Table 4 Cost (in USD) analysis during the first 6 months of follow-up and for the entire 12 months of follow-up

	Group N				Group M			
	n	Mean (SD)	95% CI	% of total medical costs	*n*	Mean (SD)	95% CI	% of total medical costs
First 6 months of follow-up								
Total medical costs	50,284	28,788 (18,061)	28,630–28,945		27,906	32,866 (20,222)	32,629–33,104	
Outpatient costs	49,598	18,556 (15,097)	18,423–18,689	64.5%	27,246	18,220 (15,398)	18,037–18,403	55.4%
Inpatient costs	32,117	16,415 (17,007)	16,229–16,601	57.0%	20,912	20,120 (20,889)	19,837–20,403	61.2%
Defined MTT costs	50,284	16,541 (14,113)	16,418–16,665	57.5%	27,906	16,689 (14,536)	16,518–16,859	50.8%
Moisturizer costs	0	–	–		20,656	35 (65)	34–36	0.1%
Other drug costs	49,564	5434 (6788)	5374–5494	18.9%	27,864	6500 (7709)	6409–6590	19.8%
Radiotherapy costs	2893	2351 (1259)	2305–2397	8.2%	2176	2398 (1406)	2339–2458	7.3%
Entire 12 months of follow-up								
Total medical costs	50,284	44,814 (29,634)	44,555–45,073	100.0%	27,906	53,797 (32,183)	53,419–54,174	100.0%
Outpatient costs	50,175	30,856 (26,524)	30,624–31,088	68.9%	27,774	31,358 (25,857)	31,054–31,662	58.3%
Inpatient costs	34,939	20,185 (22,313)	19,951–20,419	45.0%	22,995	27,411 (29,834)	27,026–27,797	51.0%
Defined MTT costs	50,284	25,838 (24,192)	25,627–26,050	57.7%	27,906	26,872 (23,761)	26,593–27,151	50.0%
Moisturizer costs	0	–	–		27,906	53 (108)	51–54	0.1%
Other drug costs	49,808	8551 (11,271)	8452–8650	19.1%	27,898	10,880 (12,825)	10,730–11,031	20.2%
Radiotherapy costs	4284	2478 (1321)	2438–2517	5.5%	3517	2525 (1449)	2477–2573	4.7%

SD standard deviation, *CI* confidence interval, *MTT* molecular targeted therapy

.

Moisturizer Utilization Pattern

The proportion of patients prescribed moisturizers was 35.7% among patients prescribed MTT during the study period. The proportion varied greatly among the MTT groups. The proportion of moisturizer users was the highest in the EGFR inhibitor group (71.4%) followed by the multikinase inhibitor group (50.2%), immune checkpoint inhibitor group (42.1%), and VEGF inhibitor group (40.2%). The proportion of users was low in the anti-CD20 antibody group (23.2%) and BCR-ABL inhibitor group (15.4%). The proportion of moisturizer users over time showed an increasing trend (31.6% in 2011 to 39.1% in 2018), and the proportion of moisturizer users in the EGFR inhibitor group increased from 53.5% to 74.7% during the same period. Moreover, in the 2018 data, the proportion of moisturizer users in the BCR-ABL inhibitor group, which was the lowest among the MTT groups, reached 21.1%. These findings suggest that moisturizer use has become common, not only with the use of EGFR inhibitors, which commonly cause skin disorders owing to their mechanisms of action, but also with the use of other anticancer drugs, where the mechanism by which they cause skin disorders is unclear. The proportion of EGFR inhibitors among the MTT groups actually decreased (13.8% in 2012 to 5.8% in 2018), which suggests that the increasing trend in moisturizer use was not caused by changes in the type of MTT being prescribed.

Variations in the Moisturizer Utilization Pattern

In Group M, 31.5% of the patients were prescribed moisturizers within 1 month after beginning MTT. However, the start of prescriptions was not limited to a certain period. Frequent symptoms of skin disorder differ depending on the MTT. Symptoms such as acneiform folliculitis peaked approximately 2 weeks after beginning MTT, while other symptoms, such as xerosis and paronychia, mainly developed after 28 days or later [10, 11]. These findings suggest that variable timing of initiating moisturizer use in the present analysis reflects variable timing in the onset of skin disorders.

Overall Budget Impact of Moisturizers

When drugs were compared according to their unit prices, there was a large difference between moisturizers and MTTs. Therefore, when we evaluated medical costs and drug costs per patient, the contribution of moisturizer costs was small. Specifically, the analysis of total medical costs at 6 months and 12 months showed that the difference in medical costs between Group M and Group N was USD 4078 (JPY 0.467 million) at 6 months and USD 8983 (JPY 1.029 million) at 12 months. However, the difference in moisturizer costs was USD 35 (JPY 4008) at 6 months and USD 53 (JPY 6033) at 12 months, which accounted for 0.1% of the total medical costs and only 0.59% in the difference in the total costs at 12 months.

The total medical costs for users of anticancer drugs in Japan, calculated by dividing the total medical costs of users of anti-cancer drugs in the MDV database by 22%, which is the patient coverage of this database, was USD 17.1 billion (JPY 1.96 trillion; 1.174 trillion for nonusers of moisturizers and 0.782 trillion for users); moisturizer costs accounted for USD 6.63 million (JPY 760 million). Therefore, conceivably, the medical costs of prescribed moisturizers in cancer treatment is extremely low. The main factors causing the high medical costs in Group M were extended hospitalization and increased costs of drugs other than moisturizers.

Limitations

The present study used commercially available claims data from DPC hospitals and did not capture treatments performed in non-DPC hospitals or clinics. In addition, nonprescription moisturizers such as over-the-counter moisturizers were not included. Follow-up of patients who were transferred to other medical institutions during treatment was also not possible. In Japan, unlike in other countries, the availability of a health insurance claims

database at the national level is extremely limited. However, some drug utilization studies using commercially available claims data have been reported despite the limitations [12–14]. We expect that similar analyses will be performed in the future using a broader database, to improve the generalizability of the findings in this study, if such a database becomes available.

The present study was not a comprehensive analysis of cancer treatment. We analyzed only patients with cancer who were prescribed MTT. Some MTTs, for example, EGFR inhibitors, are expected to cause skin disorders frequently because of their mechanisms of action. Therefore, the need for moisturizers in patients receiving MTT is higher than for patients receiving other anticancer drugs, which was why patients receiving MTT were chosen as the first cohort. However, because cytotoxic anticancer drugs can also cause skin disorders as an adverse event, broader studies analyzing patients receiving a wide variety of anticancer drugs are desirable.

Dermatological diagnoses caused by MTTs could not be identified because this database does not contain relationships between diagnoses and prescribed drugs. When we selected the patients for this study cohort from the source cohort, we excluded patients who were prescribed moisturizers before initiating MTT. This criterion was set to exclude the use of moisturizers to treat skin disorders not caused by anticancer drugs. However, this criterion also excluded patients prescribed moisturizers prophylactically and those who were already being treated with other anticancer drugs and who were prescribed moisturizers for skin disorders. Because of the stricter inclusion/exclusion criteria we set to identify only patients strongly associated with skin disorders caused by MTT, we expect that the number of patients using moisturizers in clinical practice is higher.

CONCLUSION

In this study, we analyzed moisturizer use in patients treated with MTT, using a commercially available claims database. The proportion of patients treated with MTT who used moisturizers was 35.7%, and the proportion varied among the MTT groups. The proportion of patients who were prescribed moisturizers increased over time. We also saw variations in the prescription length in days and the amount of moisturizers prescribed. Thus, we believe that moisturizers were used according to each patient's condition.

Regarding the medical costs required for MTT treatment, the medical costs in Group M were higher than for Group N by USD 8983 (JPY 1.029 million) at 12 months. However, most of the costs resulted from costs not related to the moisturizer costs (e.g., costs for hospitalization and other drugs). The difference in costs that can be associated with moisturizers was USD 53 (approximately JPY 6000). Moisturizers accounted for 0.59% of the difference in the total medical costs in Group N and 0.1% of the total medical costs. We determined that the cost and use of moisturizers may contribute to continuation of MTT treatment.

ACKNOWLEDGEMENTS

Funding. This study and the Rapid Service Fee were funded by Maruho Co., Ltd.

Medical Writing, Editorial, and Other Assistance. Language editing assistance was provided by ASCA Corporation, funded by Maruho Co., Ltd.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. All authors contributed to the study conception and design. Statistical analyses were performed by Yoshie Onishi and Anastasiia Motrunich. The first draft of the manuscript in Japanese was written by Ataru Igarashi and Yoshio Kiyohara. All authors read and approved the final manuscript.

Disclosures. Creativ-Ceutical K.K., Tokyo, Japan was paid to conduct the study. Ataru Igarashi and Yoshio Kiyohara received lecture/consultation fees from Maruho Co., Ltd.; Anastasiia Motrunich and Yoshie Onishi are employee of Creativ-Ceutical.; Akira Kanakubo and Momoyo Kishida are employees of Maruho Co., Ltd.; Lida Teng and Toshiya Matsuzaki have nothing to disclose.

Compliance with Ethics Guidelines. MDV database is comprised of secondary, unlikable anonymized data, institutional review board approval was not required in the study.

Data Availability. Not available because the datasets are commercial data of Medical Data Vision, Co., Ltd.

REFERENCES

1. Lacouture ME, Anadkat MJ, Bensadoun RJ, et al. Clinical practice guidelines for the prevention and treatment of EGFR inhibitor-associated dermatologic toxicities. Support Care Cancer. 2011;19:1079–95.

2. National Cancer Center Japan, ed. 2016 Clinical guide of appearance care for people receiving cancer treatment [in Japanese]. Tokyo, Kanehara & Co., Ltd; 2016

3. Grande R, Narducci F, Bianchetti S, et al. Pre-emptive skin toxicity treatment for anti-EGFR drugs: evaluation of efficacy of skin moisturizers and lymecycline. A phase II study. Support Care Cancer. 2013;21:1691–5.

4. Watanabe S, Nakamura M, Takahashi H, et al. Dermopathy associated with cetuximab and panitumumab: investigation of the usefulness of moisturizers in its management. Clin Cosmet Investig Dermatol. 2017;11:353–61.

5. Sekiguchi K, Ogita M, Akahane K, et al. Randomized, prospective assessment of moisturizer efficacy for the treatment of radiation dermatitis following radiotherapy after breast-conserving surgery. Jpn J Clin Oncol. 2015;45:1146–53.

6. Sekiguchi K, Akahane K, Ogita M, et al. Efficacy of heparinoid moisturizer as a prophylactic agent for radiation dermatitis following radiotherapy after breast-conserving surgery: a randomized controlled trial. Jpn J Clin Oncol. 2018;48:450–7.

7. Yoshida Y, Hashimoto K, Saeki H, et al. Efficacy of a moisturizer for pruritus accompanied with asteatosis in dialysis patients: an open-label, randomized, exploratory study. Kidney Med. 2019;1:191–9.

8. Wacker B, Nagrani T, Weinberg J, Witt K, Clark G, Cagnoni PJ. Correlation between development of rash and efficacy in patients treated with epidermal growth factor receptor tyrosine kinase inhibitor erlotinib in two large phase III studies. Clin Cancer Res. 2007;13:3913–21.

9. Sugiura Y, Nemoto E, Kawai O, Ohkubo Y, Fusegawa H, Kaseda S. Skin rash by gefitinib is a sign of favorable outcomes for patients of advanced lung adenocarcinoma in Japanese patients. Springerplus. 2013;2:22.

10. Beech J, Germetaki T, Judge M, et al. Management and grading of EGFR inhibitor-induced cutaneous toxicity. Future Oncol. 2018;14:2531–41.

11. Kozuki T. Skin problems and EGFR-tyrosine kinase inhibitor. Jpn J Clin Oncol. 2016;46:291–8.

12. Sruamsiri R, Iwasaki K, Tang W, Mahlich J. Persistence rates and medical costs of biological therapies for psoriasis treatment in Japan: a real-world data study using a claims database. BMC Dermatol. 2018;18:5.

13. Igarashi A, Fujita H, Arima K, et al. Health-care resource use and current treatment of adult atopic

dermatitis patients in Japan: a retrospective claims database analysis. J Dermatol. 2019;46:652–61.

14. Imafuku S, Matsuki T, Mizukami A, et al. Burden of herpes zoster in the Japanese population with immunocompromised/chronic disease conditions: results from a cohort study claims database from 2005–2014. Dermatol Ther (Heidelb). 2019;9:117–33.