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Article

Fact-Finding Survey and Exploration of Preventive Drugs for Antineoplastic Drug-Induced Oral Mucositis Using the Japanese Adverse Drug Event Report Database

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Abstract: Oral mucositis (OM) is one of the most common adverse events associated with antineoplastic drug treatment. Studies on the risk of antineoplastic drug-induced OM and its prevention are limited. We, therefore, conducted a disproportionality analysis of antineoplastic drug-induced OM and explored candidate preventive drugs for OM using the Japanese Adverse Drug Event Report (JADER) database. The JADER database showed that between April 2004 and March 2022, antineoplastic drug-related adverse events were reported in 210,822 cases, of which 2922 were OM. Forty-two drugs appeared to be associated with OM. The weibull distribution showed different patterns of time-to-onset depending on the type of antineoplastic drug administered. Cluster analyses classified antineoplastic drugs according to the typical symptoms of OM. These findings suggest that antineoplastic drug-induced OM should be monitored based on expression patterns of symptoms. Upon analyzing the inverse association, several concomitant drugs, including lenalidomide hydrate and febuxostat, were expected to be candidate preventive drugs for antineoplastic drug-induced OM. Concomitant drugs that showed an inverse association with antineoplastic drug-induced OM differed within the Anatomical Therapeutic Chemical classification. These findings could serve as a reference when considering drugs that should be prioritized to validate their prophylactic effect against antineoplastic-induced OM in the future.

Keywords: oral mucositis (OM); Japanese Adverse Drug Event Report (JADER); disproportionality analysis; weibull distribution; cluster analysis; inverse association

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1. Introduction

Oral mucositis (OM) is an inflammatory disease of the oral cavity mucosa and is one of the most common adverse events (AEs) associated with antineoplastic drugs [1–3]. It affects the quality of life of patients and their ability to tolerate treatment. The main symptoms of OM include oral pain, hemorrhage, dryness, redness, swelling of the oral mucosa, restricted mouth opening, dysarthria, dysphagia, and taste disorders, which cause extreme pain interfering with oral ingestion in severe cases. The frequency of antineoplastic drug-induced OM varies according to the type of drug administered. For example, a frequency of 65% has been documented with alkylating drugs (e.g., cyclophosphamide), plant alkaloids and other natural products (e.g., docetaxel), cytotoxic antibiotics and related substances (e.g., doxorubicin) [4]; 14–35% with antimetabolites (e.g., fluorouracil) [4]; 67% with everolimus [5]; 5–33% with sorafenib [6]; 40.5% with bevacizumab [7]; and approximately 40% with platinum drugs [4]. Chemotherapy-induced OM generally occurs 3–4 days after administration, peaks approximately 2 weeks after administration, and improves almost 3 weeks after administration [8,9]. The onset of OM induced by protein kinase inhibitors and other molecularly targeted drugs varies; however, with everolimus

and other mTOR inhibitors, OM occurs several days after administration, with a median time to onset of approximately 10 days, improving in approximately 1 week [10]. These results suggest that antineoplastic drug-induced OM should be monitored based on the expression pattern of symptoms. The primary sources of information for managing OM are package inserts of prescription drugs and clinical trials [11]. However, recent reports [12,13] have primarily included only certain antineoplastic drugs or investigated these based on meta-analyses [14]; thus, comprehensive reporting on OM induced by all antineoplastic drugs is lacking.

Effective drugs to prevent drug-induced OM are yet to be developed. In Japan, sodium gualenate hydrate, sodium bicarbonate, and other drugs are recommended by the Ministry of Health, Labor, and Welfare for prophylaxis against OM [15], but these do not include specialized drugs that can specifically prevent OM. Recent studies have reported potential preventive drugs against antineoplastic drug-induced OM. In a meta-analysis of 10,514 randomized subjects in 131 trials, aloe vera, amifostine, cryotherapy, granulocyte-colony stimulating factor, intravenous glutamine, honey, keratinocyte growth factor, laser, polymyxin/tobramycin/amphotericin antibiotic pastille/paste, and sucralfate provided significant prevention against OM [11]. There is also reported that composed herbal extract, applied in the form of a mouthwash and in the form for topical application with benzocaine content showed remission of oral mucositis [16]. In a multicenter, single-arm phase II study (SWISH study) of patients with breast cancer who received everolimus and exemestane, a dexamethasone mouthwash reduced the incidence of grade 2 or higher OM [12]. However, this evidence is based on limited interventions with specific antineoplastic drugs and is not universally applicable to all antineoplastic drugs. The number of reports regarding OM induced by new types of antineoplastic drugs, such as molecular targeted drugs and immune checkpoint inhibitors, has also increased [17–19]. Therefore, there is a growing need to develop drugs capable of preventing OM.

Currently, studies using pharmacovigilance databases are underway worldwide. These studies evaluate the association between drugs and AEs, identify the time from the onset of AE, and investigate drug repositioning [20]. The Japanese Adverse Drug Event Report (JADER) published by the Pharmaceuticals and Medical Devices Agency (PMDA) has been used to investigate the relationship between drugs and AEs [21,22].

For successful antineoplastic drug therapy, evaluating the risk of OM for each antineoplastic drug and identifying preventive drugs is crucial. In the current study, we aimed to measure the disproportionality of antineoplastic drug-induced OM and analyze the expression pattern of OM. The results suggest that antineoplastic drug-induced OM should be monitored based on the expression pattern of symptoms. These findings will provide useful reference information for the management of OM. We also explored candidate preventive drugs against OM using the JADER database. The result showed that several concomitant drugs, including lenalidomide hydrate and febuxostat, are potential candidates for antineoplastic-induced OM prevention. The findings serve as a reference when considering drugs that should be prioritized to validate their prophylactic effect against OM in patients treated with antineoplastic drugs.

2. Materials and Methods

2.1. Data Sources

JADER is the Adverse Drug Reaction Database provided by the PMDA, documenting case reports of adverse drug reactions. Adverse drug reaction reports, which can be downloaded and used freely, are updated monthly and published on the PMDA website (http://www.pmda.go.jp/; accessed on 15 July 2022). JADER data are divided into four tables: demographic information pertaining to the patient, sex, age, and reporting year (demo); drug information, including prescribed drug, dosage, route, the reason for use, and start and end dates of administration (drug); AE, including the type of AE, outcome, and date of onset (reac); and primary disease (hist). Each reported item could be associated with an identification number. Data was downloaded on 15 July 2022 and included data

reported from April 2004 to March 2022. Drugs listed in the dataset table were classified into suspected, concomitant, or interacting drugs. Herein, we used all drug classifications to investigate the actual relevance of drugs and OM and to evaluate the inverse association between potentially preventive drugs and antineoplastic-induced OM. Overlapping drugs with the same case identification number (ID) were excluded from the analysis. In the "reac" table, the adverse drug reactions were registered based on the Preferred Terms of Medical Dictionary for Regulatory Activities/Japan version; MedDRA/J. OM-related AEs are listed in Supplementary Table S1 online. Data were extracted using MedDRA/J ver.25.1 (https://www.jmo.pmrj.jp/; accessed on 15 July 2022). Overlapping cases of OM with the same ID were excluded from the analysis.

2.2. Selection of Antineoplastic Drugs

We included antineoplastic drugs classified as antineoplastic drugs (L01) in the Anatomical Therapeutic Chemical (ATC) classification system (https://www.kegg.jp/brite/jp08303/A10BK02; accessed on 15 July 2022). From the following standardized MedDRA Querie (SMQ)s, we determined the antineoplastic indication using primary disease data [23]: malignancy-related conditions (SMQ 20000092), tumor markers (SMQ 20000094), malignant tumors including gastric, colorectal, lung, and hepatic cancers (SMQ 20000194), breast malignant tumors (SMQ 20000198), ovarian malignant tumors (SMQ 20000200), prostate malignant tumors (SMQ 20000202), skin malignant tumors (SMQ 20000204), uterine and fallopian tube malignant tumors (SMQ 20000206), and malignant lymphomas (SMQ 20000215).

2.3. Statistical Analysis

The reporting odds ratio (ROR) was calculated to evaluate the association between OM and antineoplastic drugs. The ROR was calculated using a two-by-two contingency table (Supplementary Figure S1 online), which is widely used as a signal indicator in the Adverse Drug Reaction Database [24]. The two-by-two contingency table cannot be calculated with zero cells, and the estimation becomes unstable when the cell frequency is small. Therefore, to correct this bias, 0.5 was added to all cells (Haldane-Anscombe 1/2 correction) [25,26]. In the current study, we determined the association between antineoplastic drugs and OM when the ROR showed a lower limit of 95% confidence interval (CI) > 1 and a p-value < 0.05, as determined by Fisher's exact test [24]. We also created a volcano plot using the natural logarithm of the ROR (ln ROR) and the normal logarithm of the p-value ($-\log[p]$) to visually evaluate the association between OM and antineoplastic drugs [23,27].

For the time to onset analysis, distinct from the other analysis, we extracted the "suspected drug" from the "drug" table. The start date of administration was defined as the date of the first administration before the onset of OM. The number of days until the appearance of OM was calculated as follows: [(onset date)−(start date of administration)] plus 1 day. If the number of days to the onset was greater than 365, it was calculated as 365 days. Additionally, the pattern of onset time was classified using the shape parameter β of the Weibull distribution. Weibull parameters were used for the time-to-onset analysis to investigate the time-course hazards of AEs. When β is equal to 1 (random failure type), the hazard is estimated to remain constant over time. When β < 1 and the 95% CI of β excluded the value 1 (early failure type), the hazard is estimated to decrease over time. When β > 1 and the 95% CI of β excluded the value of 1 (wear-out failure type), the hazard is estimated to increase over time [28].

Hierarchical cluster analyses were performed to classify OM-related AEs induced by antineoplastic drugs. We examined 42 antineoplastic drugs with OM and 11 OM-related AEs with ≥10 cases reported. OM-related AEs with <10 cases were excluded for the cluster analysis. We calculated the ROR from two contingency tables for 11 AEs and 42 drugs. We then created a dendrogram based on the presence or absence of disproportionality and evaluated the distribution of drugs that showed disproportionality to each AE using the Ward method with Euclidean distance [29].

Among drugs administered concomitantly with antineoplastic drugs, we examined those with total reports of ≥100 AEs. The ROR and *p*-values were calculated for each drug using Fisher's exact test to establish a volcano plot. Herein, we defined an inverse association between concomitant drugs and antineoplastic-induced OM when the ROR showed an upper limit of 95% CI < 1 and a *p*-value < 0.05, according to Fisher's exact test [24].

All statistical analyses were performed using JMP Pro17 software (SAS Institute Inc., Cary, NC, USA).

3. Results

The total number of cases registered in JADER between April 2004 and March 2022 was 775,555. In total, 210,822 cases involved antineoplastic drug-induced AEs, of which 2922 were OM (Figure 1).

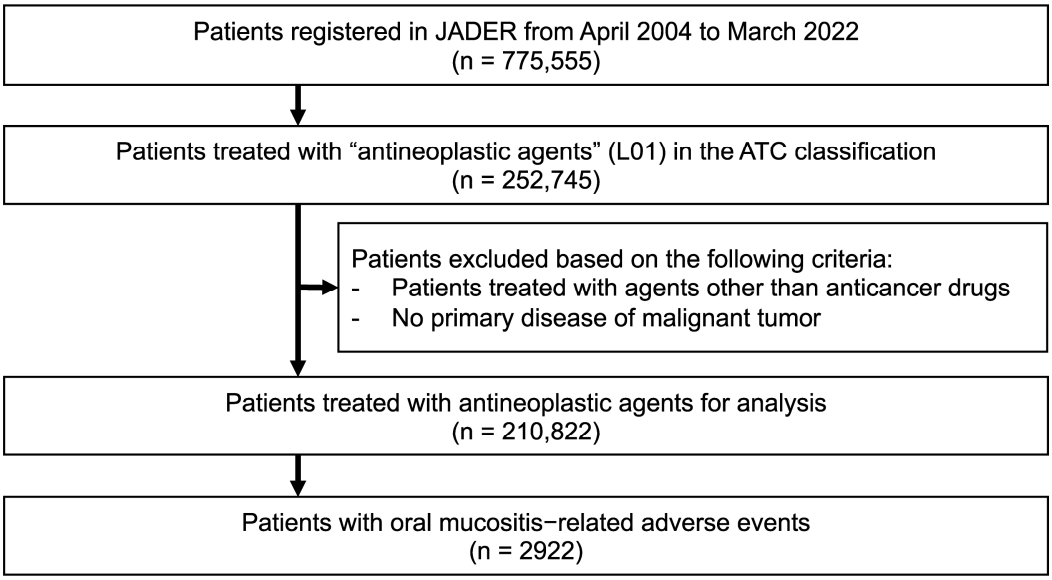

Figure 1. Flowchart of case selection. JADER: Japanese Adverse Drug Event Report. ATC: Anatomical Therapeutic Chemical.

The characteristics of the patients treated with antineoplastic drugs are shown in Supplementary Table S2 (online). The sex distribution was as follows: 40.3% were females, 54.6% were males, and 5.1% were unknown. Regarding age, 29.1%, of patients were 70–79 years of age, and 28.0% were 60–69 years of age. According to the ATC classification, monoclonal antibodies and antibody-drug conjugates (L01F) were the most prevalent (36.3%). Among the patients with OM, 47.1% were females, 49.9% were males, and 3.1% were others or unknown. Regarding age, 29.1% of patients were 60–69 years of age, and 28.9% were 70–79 years of age. According to the ATC classification, antimetabolites (L01B) were the most prevalent (51.2%).

The number of cases and ROR for antineoplastic drug-induced OM are shown in Table 1. Figure 2 presents a volcano plot of the association between OM and antineoplastic drugs. As shown in Table 1 and Figure 2, 42 drugs were associated with OM. The most frequently reported drugs with OM were tegafur/gimeracil/oteracil potassium (523 reports; 17.9%), fluorouracil (333 reports; 11.4%), cisplatin (305 reports; 10.4%), everolimus (264 reports; 9.0%), capecitabine (222 reports; 7.6%), and oxaliplatin (209 reports; 7.2%).

Table 1. Number of reports and reporting odds ratios for oral mucositis.

ATC [a] Category (ATC [a] Code)	Antineoplastic Agents	Case (*n*)	Total (*n*)	ROR [b] (95% CI [c])	*p*-Value
Total		2922	210,822		
Alkylating agents (L01A)	Melphalan *	133	3370	6.99 (5.86–8.33)	<0.0001
	Busulfan *	118	1879	11.39 (9.43–13.75)	<0.0001
	Cyclophosphamide *	85	8307	1.73 (1.40–2.15)	<0.0001
	Thiotepa *	28	360	14.25 (9.71–20.92)	<0.0001
	Bendamustine	19	2665	1.22 (0.78–1.91)	0.4490
	Ranimustine *	12	498	4.26 (2.43–7.47)	0.0001
	Ifosfamide	9	1683	0.94 (0.50–1.78)	0.8740
	Temozolomide	7	1678	0.74 (0.36–1.52)	0.4270
	Streptozocin	2	136	1.12 (0.88–10.75)	0.1970
	Dacarbazine	0	954	–	–
	Carmustine	0	538	–	–
	Nimustine	0	489	–	–
	Larotrectinib	0	5	–	–
	Carboquone	0	5	–	–
Antimetabolites (L01B)	Tegafur/gimeracil/oteracil potassium *	523	9872	10.30 (9.39–11.31)	<0.0001
	Fluorouracil *	333	18,661	3.16 (2.83–3.54)	<0.0001
	Capecitabine *	222	6182	6.43 (5.61–7.38)	<0.0001
	Methotrexate *	198	4091	8.76 (7.57–10.13)	<0.0001
	Tegafur and uracil *	90	2285	6.93 (5.61–8.57)	<0.0001
	Fludarabine *	83	3110	4.63 (3.71–5.76)	<0.0001
	Cytarabine *	77	4971	2.65 (2.11–3.32)	<0.0001
	Pralatrexate *	73	238	74.60 (56.59–98.33)	<0.0001
	Gemcitabine	44	6889	1.08 (0.80–1.45)	0.6390
	Pemetrexed	26	5290	0.83 (0.57–1.22)	0.3710
	Azacitidine	11	2651	0.72 (0.40–1.28)	0.2560
	Clofarabine *	9	295	5.49 (2.88–10.49)	0.0001
	Mercaptopurine *	5	302	3.06 (1.32–7.11)	0.0370
	Trifluridine and tipiracil hydrochloride	3	666	0.87 (0.30–2.49)	0.8040
	Nelarabine	3	202	2.90 (1.02–8.35) *	0.1230
	Cladribine	1	171	1.45 (0.29–7.26)	1.0000
	Tegafur	1	51	4.91 (0.97–24.93)	0.2650
	Carmofur	0	8	–	–
	Decitabine	0	1	–	–

Table 1. *Cont.*

ATC [a] Category (ATC [a] Code)	Antineoplastic Agents	Case (*n*)	Total (*n*)	ROR [b] (95% CI [c])	*p*-Value
Plant alkaloids and other natural products (L01C)	Irinotecan *	173	10,253	2.92 (2.50–3.40)	<0.0001
	Docetaxel *	170	10,441	2.81 (2.41–3.28)	<0.0001
	Etoposide *	123	7583	2.78 (2.33–3.33)	<0.0001
	Paclitaxel	81	11,997	1.13 (0.91–1.41)	0.2840
	Vincristine	47	7353	1.08 (0.81–1.43)	0.6490
	Vinorelbine	13	1223	1.85 (1.08–3.16)	0.0592
	Vinblastine	4	758	0.99 (0.39–2.49)	1.0000
	Topotecan	0	482	–	–
	Vindesine	0	482	–	–
	Trabectedin	0	258	–	–
	Cabazitaxel	0	2	–	–
Cytotoxic antibiotics and related substances (L01D)	Doxorubicin *	187	8715	3.75 (3.23–4.34)	<0.0001
	Dactinomycin *	27	398	12.31 (8.35–18.15)	<0.0001
	Epirubicin	16	2658	1.03 (0.64–1.68)	0.9000
	Amrubicin	10	1364	1.28 (0.70–2.36)	0.4810
	Idarubicin	9	788	2.02 (1.06–3.83)	0.0602
	Mitoxantrone *	8	582	2.45 (1.24–4.82)	0.0262
	Pirarubicin	6	1550	0.70 (0.32–1.50)	0.4060
	Mitomycin	5	555	1.65 (0.71–3.83)	0.3970
	Daunorubicin	4	1150	0.65 (0.26–1.64)	0.3400
	Bleomycin	2	791	0.52 (0.15–1.81)	0.3480
	Aclarubicin	0	360	–	–
Protein kinase inhibitors (L01E)	Everolimus *	264	3623	13.74 (12.08–15.63)	<0.0001
	Sunitinib *	111	4425	4.35 (3.60–5.27)	<0.0001
	Palbociclib *	73	2466	5.14 (4.07–6.50)	<0.0001
	Lapatinib *	70	865	14.86 (11.63–19.00)	<0.0001
	Sorafenib *	69	6031	1.94 (1.53–2.46)	<0.0001
	Erlotinib *	63	3378	3.20 (2.49–4.10)	<0.0001
	Afatinib *	44	1020	7.60 (5.62–10.28)	<0.0001
	Axitinib *	37	1919	3.31 (2.39–4.58)	<0.0001
	Temsirolimus *	29	726	7.03 (4.86–10.18)	<0.0001
	Gefitinib	21	3179	1.13 (0.74–1.72)	0.6440
	Lenvatinib	18	2596	1.19 (0.75–1.88)	0.5230
	Imatinib	16	4821	0.57 (0.35–0.92)	0.0114
	Osimertinib	12	2699	0.77 (0.44–1.34)	0.3800
	Regorafenib	11	2280	0.84 (0.47–1.50)	0.5860
	Pazopanib	11	2079	0.92 (0.51–1.64)	0.7770
	Cabozantinib	11	1164	1.65 (0.92–2.95)	0.1270
	Ibrutinib	5	574	1.60 (0.69–3.70)	0.4050
	Nilotinib	3	2316	0.25 (0.09–0.71)	0.0010
	Dasatinib	3	2083	0.28 (0.10–0.79)	0.0026

Table 1. *Cont.*

ATC [a] Category (ATC [a] Code)	Antineoplastic Agents	Case (*n*)	Total (*n*)	ROR [b] (95% CI [c])	*p*-Value
Protein kinase inhibitors (L01E)	Trametinib	3	583	1.00 (0.35–2.85)	1.0000
	Crizotinib	2	1272	0.33 (0.09–1.12)	0.0421
	Gilteritinib	2	734	0.56 (0.16–1.95)	0.3400
	Dabrafenib	2	570	0.73 (0.21–2.52)	0.7810
	Lorlatinib	2	317	1.31 (0.38–4.55)	0.7160
	Dacomitinib *	2	30	14.51 (3.98–52.89)	0.0140
	Nintedanib	1	918	0.27 (0.05–1.33)	0.0516
	Ponatinib	1	793	0.31 (0.06–1.55)	0.1020
	Cediranib	1	51	4.91 (0.97–24.93)	0.2650
	Ruxolitinib	0	1417	–	–
	Abemaciclib	0	624	–	–
	Bosutinib	0	527	–	–
	Alectinib	0	473	–	–
	Ceritinib	0	379	–	–
	Encorafenib	0	341	–	–
	Binimetinib	0	319	–	–
	Brigatinib	0	141	–	–
	Vemurafenib	0	136	–	–
	Entrectinib	0	123	–	–
	Tepotinib	0	72	–	–
	Vandetanib	0	71	–	–
	Quizartinib	0	50	–	–
	Capmatinib	0	22	–	–
	Acalabrutinib	0	13	–	–
	Selpercatinib	0	10	–	–
	Pemigatinib	0	6	–	–
Monoclonal antibodies and antibody-drug conjugates (L01F)	Bevacizumab *	169	14,834	1.95 (1.67–2.27)	<0.0001
	Cetuximab *	126	3973	5.56 (4.65–6.65)	<0.0001
	Panitumumab *	91	2387	6.70 (5.43–8.27)	<0.0001
	Trastuzumab *	64	4383	2.49 (1.94–3.19)	<0.0001
	Nivolumab	61	16,378	0.62 (0.48–0.80)	0.0001
	Ramucirumab *	53	3562	2.54 (1.93–3.33)	<0.0001
	Rituximab	48	8240	0.98 (0.74–1.30)	0.8860
	Pembrolizumab	43	9628	0.75 (0.55–1.01)	0.0465
	Atezolizumab	27	4180	1.10 (0.75–1.60)	0.6870
	Ipilimumab	20	7507	0.45 (0.29–0.70)	<0.0001
	Pertuzumab	11	1548	1.24 (0.69–2.21)	0.5100
	Mogamulizumab	8	704	2.02 (1.03–3.97)	0.0797
	Avelumab *	7	377	3.35 (1.63–6.91)	0.0084
	Gemtuzumab ozogamicin	5	739	1.24 (0.54–2.87)	0.6360
	Obinutuzumab	4	905	0.83 (0.33–2.08)	0.8270

Table 1. *Cont.*

ATC [a] Category (ATC [a] Code)	Antineoplastic Agents	Case (*n*)	Total (*n*)	ROR [b] (95% CI [c])	*p*-Value
Monoclonal antibodies and antibody-drug conjugates (L01F)	Polatuzumab vedotin	3	527	1.10 (0.39–3.16)	1.0000
	Necitumumab *	3	102	5.82 (2.00–16.91)	0.0240
	Enfortumab vedotin	2	176	2.37 (0.68–8.26)	0.2860
	Durvalumab	1	2244	0.11 (0.02–0.55)	<0.0001
	Daratumumab	1	1342	0.18 (0.04–0.92)	0.0067
	Blinatumomab	1	644	0.39 (0.08–1.91)	0.1980
	Inotuzumab ozogamicin	1	274	0.91 (0.18–4.51)	1.0000
	Brentuximab vedotin	0	1493	–	–
	Elotuzumab	0	1089	–	–
	Trastuzumab emtansine	0	619	–	–
	Trastuzumab deruxtecan	0	310	–	–
	Isatuximab	0	251	–	–
	Ofatumumab	0	107	–	–
	Dinutuximab beta	0	17	–	–
	Olaratumab	0	1	–	–
Other antineoplastic agents (L01X)	Cisplatin *	305	14,308	3.79 (3.37–4.26)	<0.0001
	Oxaliplatin *	209	13,643	2.65 (2.31–3.05)	<0.0001
	Carboplatin *	118	14,283	1.39 (1.16–1.67)	0.0008
	Eribulin *	45	1238	6.36 (4.72–8.56)	<0.0001
	Asparaginase	9	1319	1.20 (0.63–2.27)	0.5940
	Niraparib	6	701	1.55 (0.71–3.35)	0.3250
	Hydroxycarbamide	5	1165	0.78 (0.34–1.81)	0.5700
	Procarbazine	3	465	1.25 (0.44–3.58)	0.7610
	Tretinoin	3	362	1.61 (0.56–4.62)	0.4840
	Bortezomib	2	4088	0.10 (0.03–0.35)	<0.0001
	Olaparib	2	1442	0.29 (0.08–0.99)	0.0156
	Mitotane	2	144	2.90 (0.83–10.14)	0.2150
	Ixazomib	1	1459	0.17 (0.03–0.84)	0.0032
	Estramustine	1	679	0.37 (0.07–1.81)	0.2040
	Arsenic trioxide	1	477	0.52 (0.10–2.59)	0.5420
	Vorinostat	1	103	2.42 (0.48–12.14)	0.4630
	Carfilzomib	0	1182	–	–
	Venetoclax	0	599	–	–
	Panobinostat	0	578	–	–
	Anagrelide	0	357	–	–
	Romidepsin	0	232	–	–
	Aminolevulinic acid	0	159	–	–

Table 1. *Cont.*

ATC [a] Category (ATC [a] Code)	Antineoplastic Agents	Case (*n*)	Total (*n*)	ROR [b] (95% CI [c])	*p*-Value
Other antineoplastic agents (L01X)	Bexarotene	0	118	–	–
	Tisagenlecleucel	0	78	–	–
	Aflibercept	0	49	–	–
	Pentostatin	0	24	–	–
	Denileukin diftitox	0	20	–	–
	Porfimer sodium	0	16	–	–
	Veliparib	0	2	–	–
	Glasdegib	0	1	–	–

[a] ATC: Anatomical Therapeutic Chemical. [b] ROR: Reporting odds ratio. [c] CI: Confidence interval. * Significant ROR (ROR ≥ 1, Lower limit of the 95% CI corresponding to the ROR ≥ 1, and *p*-value < 0.05.).

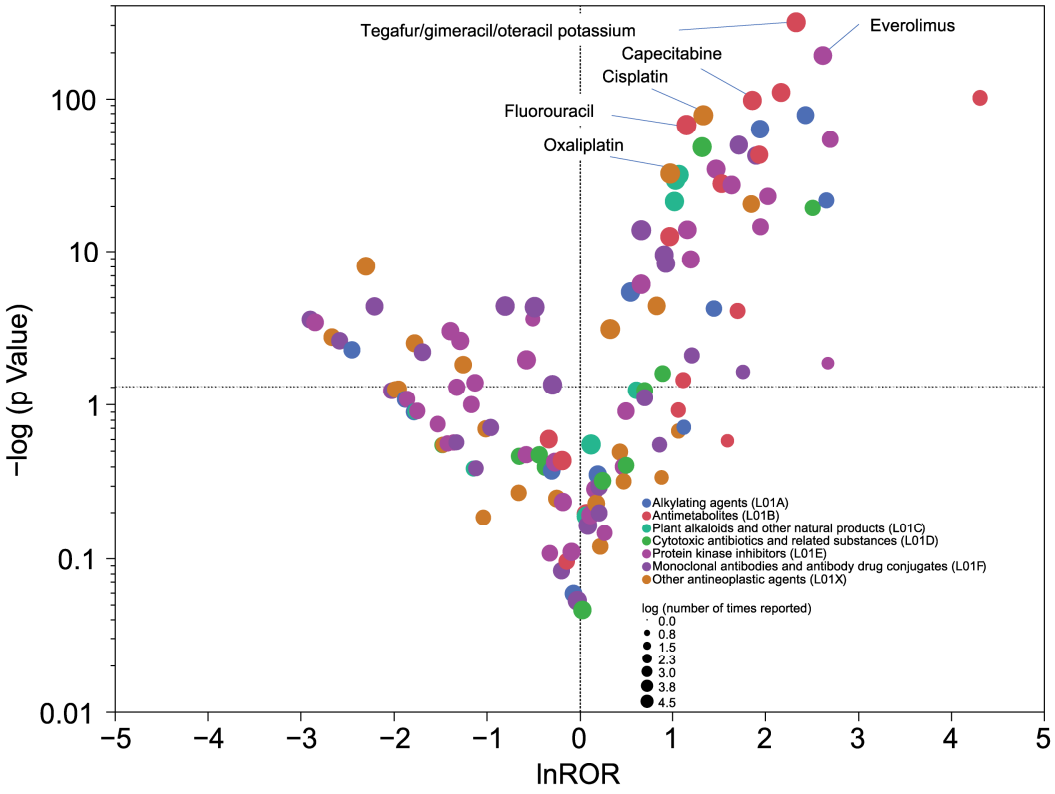

Figure 2. Antineoplastic drugs associated with oral mucositis-related adverse events. The X-axis shows the natural logarithm of the reported odds ratios (ln ROR), and the y-axis shows the common logarithm of the inverse *p*-value (−log (*p*-value)) from Fisher's exact test. The dotted line on the y-axis represents $p = 0.05$. The plot colors represent the number of reports in the ATC category. Plot size indicates the total number of reports. As the RORs became more positive, the tendency toward AEs increased; decreasing *p*-values indicated greater statistical significance. The upper-right portion of the plot shows the antineoplastic drugs associated with oral mucositis-related AEs. AEs, adverse events; ROR, reporting odds ratio.

Among the 42 antineoplastic drugs associated with OM, 39 drugs with two or more usable data points for both the starting date of administration and the onset date of AEs were included in the time-to-onset analysis. Figure 3 presents box plots of the time to onset. Table 2 shows the median time to onset and pattern of OM classified using the

Weibull distribution. The median time to OM onset ranged from approximately 7.0 days to 23.0 days. Considering the Weibull distribution, tegafur/gimeracil/oteracil potassium, fluorouracil, capecitabine, methotrexate, tegafur and uracil, pralatrexate, irinotecan, erlotinib, bevacizumab, trastuzumab, cisplatin, and eribulin were estimated to be early failures. Melphalan, thiotepa, ranimustine, dactinomycin, palbociclib, and avelumab were considered wear-out failures.

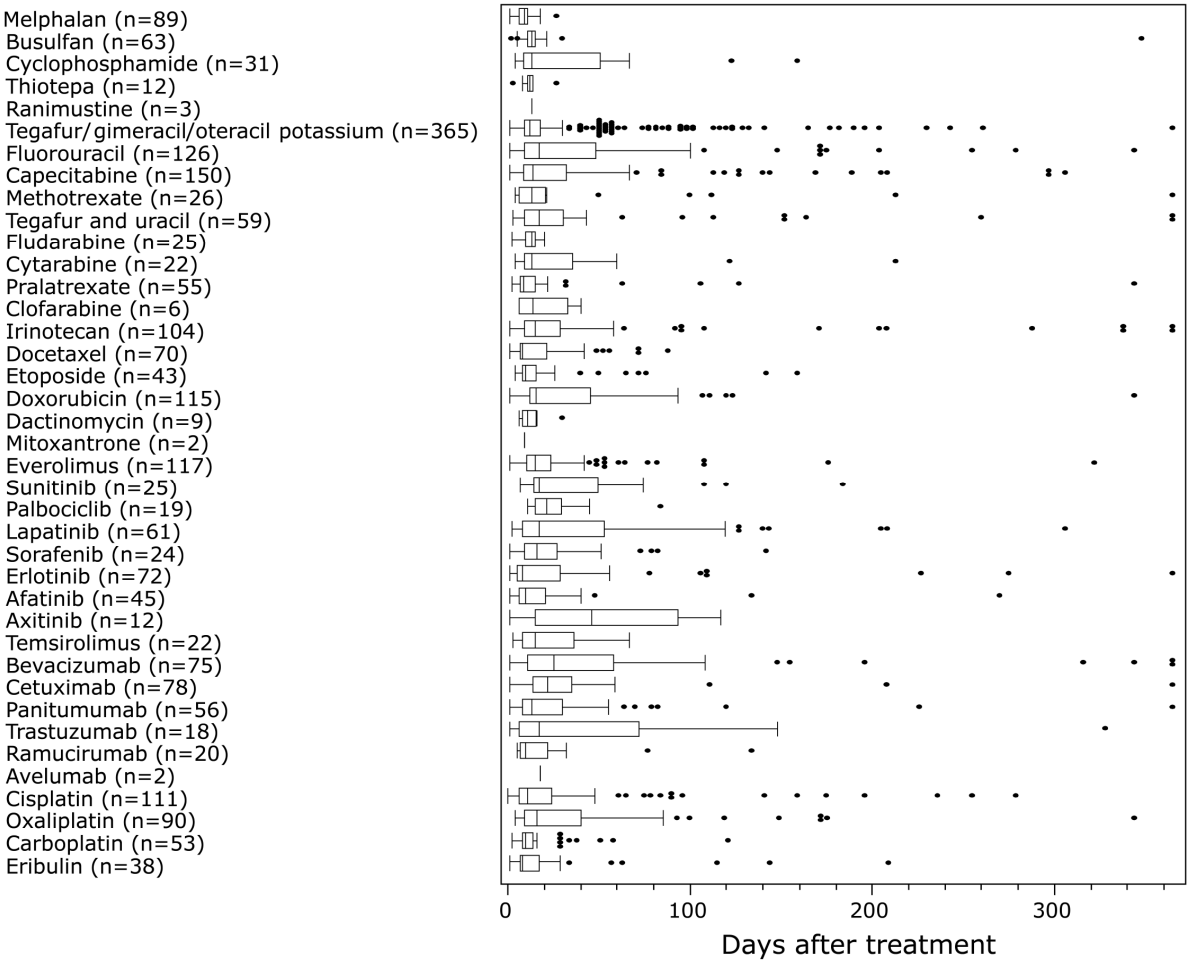

Figure 3. Box plot for time-to-onset of antineoplastic drugs associated with oral mucositis. Box plots show the 25th and 75th percentiles and medians. The whiskers present the maximum and minimum values within 1.5 times the inner quartile point's length. The values outside the box represent outliers. All data for which the number of days until the onset of oral mucositis exceeded 365 days were calculated as 365 days.

Table 2. Median values and Weibull parameters of antineoplastic drug-induced oral mucositis.

Antineoplastic Agents (ATC [a] Code)	Case	Median (25–75%) (Day)	Scale Parameter, α (95% CI [b])	Shape Parameter, β (95% CI [b])	Pattern
Alkylating agents (L01A)					
Melphalan	89	9.0 (6.0–11.0)	9.90 (8.97–10.90)	2.28 (1.94–2.63)	Wear out failure
Busulfan	63	13.0 (11.0–15.0)	17.85 (13.61–23.36)	0.98 (0.85–1.12)	Random failure
Cyclophosphamide	31	13.0 (9.0–53.0)	31.80 (21.47–46.21)	1.00 (0.76–1.28)	Random failure
Thiotepa	12	11.5 (10.25–14.0)	13.79 (10.45–17.96)	2.37 (1.49–3.40)	Wear out failure
Ranimustine	3	13.0 (8.0–13.0)	12.26 (9.19–16.31)	6.58 (1.91–16.24)	Wear out failure

Table 2. *Cont.*

Antineoplastic Agents (ATC [a] Code)	Case	Median (25–75%) (Day)	Scale Parameter, α (95% CI [b])	Shape Parameter, β (95% CI [b])	Pattern
Antimetabolites (L01B)					
Tegafur/gimeracil/oteracil potassium	416	12.0 (9.0–18.0)	23.98 (21.49–26.74)	0.94 (0.88–0.999)	Early failure
Fluorouracil	126	18.0 (9.0–49.0)	37.45 (30.23–46.16)	0.88 (0.77–0.996)	Early failure
Capecitabine	150	14.0 (8.75–32.25)	30.66 (25.01–37.43)	0.85 (0.76–0.95)	Early failure
Methotrexate	26	13.0 (6.0–20.25)	30.24 (16.49–53.99)	0.71 (0.53–0.91)	Early failure
Tegafur and uracil	59	17.0 (9.0–32.0)	39.45 (27.50–55.92)	0.78 (0.64–0.92)	Early failure
Fludarabine	25	13.0 (10.0–15.0)	17.12 (11.86–24.45)	1.18 (0.90–1.48)	Random failure
Cytarabine	22	12.5 (9.0–33.75)	30.49 (17.99–50.36)	0.90 (0.65–1.17)	Random failure
Pralatrexate	55	8.0 (6.0–15.0)	17.67 (12.39–24.99)	0.81 (0.68–0.95)	Early failure
Clofarabine	6	20.0 (6.0–65.5)	36.54 (11.54–108.38)	0.89 (0.44–1.50)	Random failure
Plant alkaloids and other natural products (L01C)					
Irinotecan	104	15.0 (9.0–29.0)	33.08 (25.18–43.18)	0.76 (0.67–0.87)	Early failure
Docetaxel	70	8.0 (7.0–21.25)	17.06 (13.48–21.42)	1.09 (0.91–1.28)	Random failure
Etoposide	43	10.0 (8.0–15.0)	21.83 (15.36–30.66)	0.94 (0.75–1.14)	Random failure
Cytotoxic antibiotics and related substances (L01D)					
Doxorubicin	115	16.0 (12.0–47.0)	32.26 (26.69–38.83)	1.04 (0.91–1.18)	Random failure
Dactinomycin	9	9.0 (8.0–15.5)	14.27 (9.53–20.89)	1.95 (1.13–2.95)	Wear out failure
Mitoxantrone	2	7.0 (5.0–9.0)	7.76 (4.06–15.31)	4.08 (0.89–11.02)	Random failure
Protein kinase inhibitors (L01E)					
Everolimus	117	15.0 (10.0–23.5)	25.11 (20.75–30.28)	1.02 (0.90–1.15)	Random failure
Sunitinib	25	18.0 (14.5–57.0)	42.33 (27.80–63.05)	1.05 (0.77–1.38)	Random failure
Palbociclib	19	22.0 (15.0–30.0)	30.72 (22.34–41.57)	1.61 (1.13–2.15)	Wear out failure
Lapatinib	61	17.0 (8.0–51.5)	38.23 (27.62–52.30)	0.85 (0.70–1.01)	Random failure
Sorafenib	24	15.5 (9.25–26.0)	28.34 (18.00–43.63)	0.99 (0.72–1.30)	Random failure
Erlotinib	72	8.0 (5.25–28.75)	23.42 (16.57–32.77)	0.73 (0.61–0.85)	Early failure
Afatinib	45	9.0 (6.0–20.5)	19.23 (13.23–27.66)	0.86 (0.70–1.02)	Random failure
Axitinib	12	53.0 (15.75–92.75)	57.70 (32.54–99.11)	1.18 (0.69–1.83)	Random failure
Temsirolimus	22	15.0 (7.75–36.0)	24.73 (16.92–35.38)	1.25 (0.88–1.70)	Random failure
Monoclonal antibodies and antibody-drug conjugates (L01F)					
Bevacizumab	75	23.0 (11.0–58.0)	47.36 (35.01–63.47)	0.82 (0.69–0.96)	Early failure
Cetuximab	78	22.0 (13.75–35.0)	30.93 (24.42–38.99)	1.02 (0.87–1.17)	Random failure
Panitumumab	56	13.5 (8.25–31.5)	30.16 (21.66–41.59)	0.87 (0.72–1.02)	Random failure
Trastuzumab	18	19.5 (6.5–89.25)	51.66 (23.62–107.87)	0.68 (0.46–0.94)	Early failure
Ramucirumab	20	10.0 (7.0–22.0)	20.85 (12.30–34.46)	0.94 (0.67–1.24)	Random failure
Avelumab	2	16.5 (15.0–18.0)	17.19 (14.06–21.22)	13.16 (2.88–35.52)	Wear out failure

Table 2. *Cont.*

Antineoplastic Agents (ATC [a] Code)	Case	Median (25–75%) (Day)	Scale Parameter, α (95% CI [b])	Shape Parameter, β (95% CI [b])	Pattern
Other antineoplastic agents (L01X)					
Cisplatin	110	11.0 (6.0–26.25)	25.06 (19.23–32.46)	0.76 (0.67–0.87)	Early failure
Oxaliplatin	90	16.0 (9.0–39.25)	33.58 (26.38–42.47)	0.93 (0.80–1.07)	Random failure
Carboplatin	53	10.0 (8.0–13.5)	16.32 (12.57–21.02)	1.13 (0.93–1.34)	Random failure
Eribulin	38	8.0 (6.75–16.75)	20.58 (13.23–31.49)	0.80 (0.63–0.98)	Early failure

[a] ATC: Anatomical Therapeutic Chemical. [b] CI: Confidence interval.

Figure 4 presents the hierarchical cluster analyses classifying antineoplastic drugs based on the presence or absence of disproportionality of OM-related AEs. Based on the dendrogram, the clusters were divided into four types. Association with stomatitis was observed in all clusters. The first cluster included fluorouracil and other drugs, and the second cluster included docetaxel and other drugs. Among alkylating agents, cyclophosphamide was included in the first cluster, and other agents were included in the second cluster. All drugs classified as cytotoxic antibiotics and related substances were included in the third cluster. These clusters showed association with pharyngeal ulceration and mouth ulceration. The fourth cluster mainly included protein kinase inhibitors (e.g., afatinib). These clusters were associated with lip erosion, stomatitis, hemorrhagic, and glossitis.

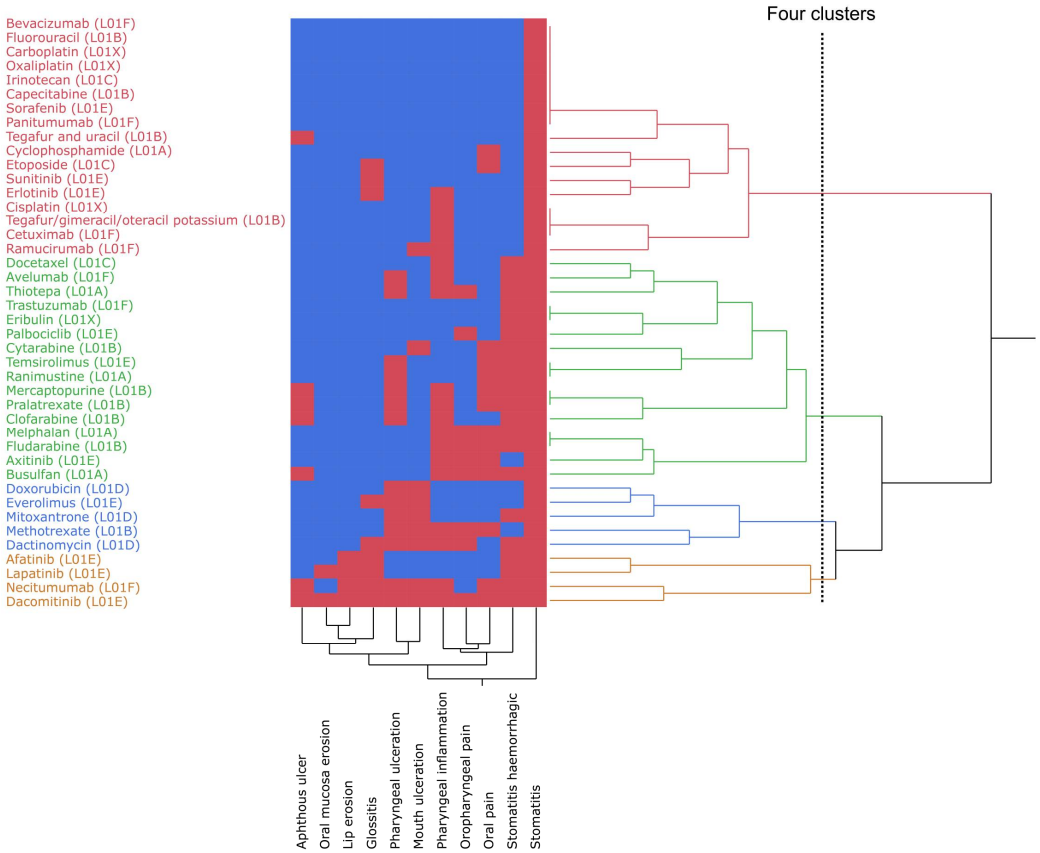

Figure 4. Classification of oral mucositis-related AEs by hierarchical cluster analysis. The dendrogram shows the relationships between 11 types of oral mucositis-related AEs. The dotted line indicates cluster separation. The color map shows the presence or absence of associated signals with AEs. Red implies "presence" and blue implies "absence". AEs, adverse events.

Treatment with concomitantly administered drugs showing an inverse association with antineoplastic-induced OM are summarized in Table 3. Twelve drug combination treatments showed inverse associations with all antineoplastic drug-induced OM. Figure 5a presents a volcano plot of the association between concomitantly administered drugs and antineoplastic drug-induced OM. Dexamethasone, prednisolone, methylprednisolone, sulfamethoxazole/trimethoprim, voriconazole, febuxostat, and lenalidomide hydrate exhibited inverse associations. However, drugs such as sodium gualenate hydrate, which is used to prevent or treat OM, did not display an inverse association with OM. Figure 5b–h present volcano plots showing the associations between concomitant medications and antineoplastic-induced OM by ATC classification. Lenalidomide hydrate showed an inverse association with OM induced by monoclonal antibodies, antibody-drug conjugates, and other antineoplastic drugs. Febuxostat showed an inverse association with OM induced by antimetabolites and other antineoplastic drugs. Dexamethasone showed an inverse association with OM induced by other antineoplastic drugs, and prednisolone showed an inverse association with OM induced by alkylating drugs, plant alkaloids, and other natural products, and cytotoxic antibiotics and related substances.

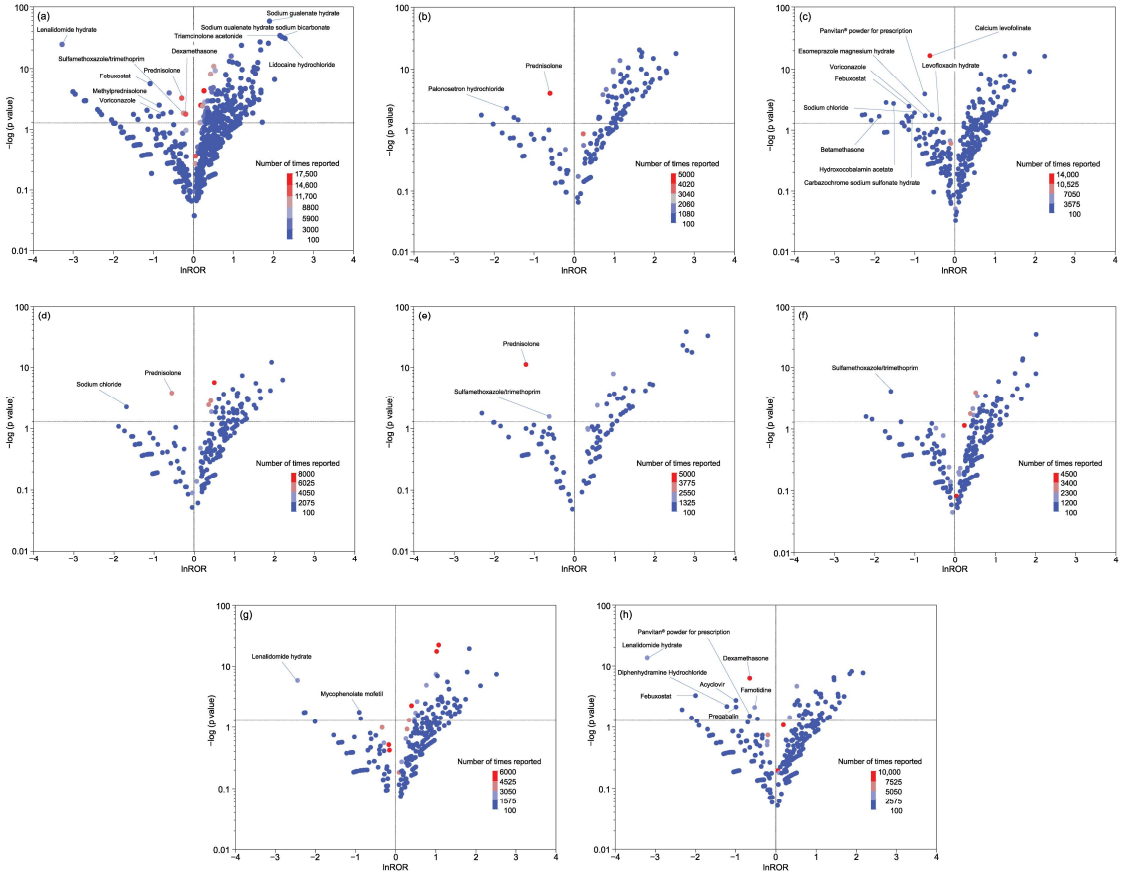

Figure 5. Drugs associated with oral mucositis-related AEs when combined with antineoplastic drugs. Combination with (**a**) all antineoplastic drugs, (**b**) alkylating drugs, (**c**) antimetabolites, (**d**) with plant alkaloids and other natural products, (**e**) with cytotoxic antibiotics and related substances, (**f**) protein kinase inhibitors, (**g**) monoclonal antibodies and antibody-drug conjugates, and (**h**) other antineoplastic drugs. The X-axis shows the natural logarithm of the reporting odds ratios (ln ROR), and the y-axis shows the common logarithm of the inverse *p*-value (−log (*p*-value)) from Fisher's exact test. The dotted line on the y-axis represents $p = 0.05$. The plot colors represent the total number of reports. As the RORs became more negative, the tendency toward AEs decreased, and decreasing *p*-values indicated greater statistical significance. The upper-left portion of the plot shows the concomitant drugs that are less frequently associated with oral mucositis-related AEs. AEs, adverse events; ROR, reporting odds ratio.

Table 3. Number of reports and reporting odds ratios for concomitant drugs with antineoplastic drugs that show a low association with oral mucositis.

ATC [a] Category (ATC Code)	Concomitant Drugs	Case (*n*)	Total (*n*)	ROR [b] (95% CI [c])	*p*-Value
All antineoplastic agents	Dexamethasone	169	14,512	0.83 (0.71–0.97)	0.0168
	Prednisolone	142	13,407	0.75 (0.63–0.89)	0.0006
	Sulfamethoxazole/trimethoprim	102	9295	0.79 (0.64–0.96)	0.0142
	Esomeprazole magnesium hydrate	35	4585	0.55 (0.39–0.77)	0.0001
	Mycophenolate mofetil	17	2170	0.58 (0.36–0.92)	0.0125
	Febuxostat	13	2798	0.34 (0.20–0.58)	<0.0001
	Methylprednisolone	9	1579	0.43 (0.23–0.81)	0.0033
	Voriconazole	8	1285	0.47 (0.24–0.93)	0.0159
	Edoxaban tosilate hydrate	5	928	0.42 (0.18–0.98)	0.0231
	Azilsartan	3	789	0.32 (0.11–0.90)	0.0089
	Basiliximab	3	720	0.35 (0.12–0.99)	0.0233
	Lenalidomide hydrate	2	4602	0.04 (0.01–0.13)	<0.0001
Alkylating agents (L01A)	Prednisolone	44	4536	0.55 (0.40–0.76)	0.0001
	Palonosetron hydrochloride	1	490	0.19 (0.04–0.93)	0.0055
Antimetabolites (L01B)	Calcium levofolinate	187	12,629	0.47 (0.46–0.63)	<0.0001
	Levofloxacin hydrate	30	1782	0.68 (0.47–0.98)	0.0296
	Panvitan® powder for prescription *	21	1787	0.47 (0.31–0.73)	0.0001
	Betamethasone	17	389	0.15 (0.03–0.76)	0.0211
	Esomeprazole magnesium hydrate	15	1085	0.57 (0.34–0.94)	0.0173
	Voriconazole	8	705	0.48 (0.24–0.94)	0.0194
	Febuxostat	4	557	0.32 (0.13–0.81)	0.0036
	Sodium chloride	4	486	0.37 (0.14–0.93)	0.0122
	Carbazochrome sodium sulfonate hydrate	3	402	0.34 (0.12–0.99)	0.0221
	Hydroxocobalamin acetate	2	453	0.22 (0.06–0.76)	0.0020
Plant alkaloids and other natural products (L01C)	Prednisolone	43	5835	0.57 (0.42–0.78)	0.0002
	Sodium chloride	1	646	0.19 (0.04–0.92)	0.0059
Cytotoxic antibiotics and related substances (L01D)	Prednisolone	26	4636	0.30 (0.20–0.45)	<0.0001
	Sulfamethoxazole/trimethoprim	11	1339	0.53 (0.30–0.97)	0.0270
Protein kinase inhibitors (L01E)	Sulfamethoxazole/trimethoprim	3	1162	0.20 (0.07–0.58)	<0.0001
Monoclonal antibodies and antibody-drug conjugates (L01F)	Lenalidomide hydrate	1	1862	0.09 (0.02–0.43)	<0.0001
	Mycophenolate mofetil	5	1485	0.40 (0.17–0.94)	0.0170

Table 3. *Cont.*

ATC [a] Category (ATC Code)	Concomitant Drugs	Case (*n*)	Total (*n*)	ROR [b] (95% CI [c])	*p*-Value
Other antineoplastic agents (L01X)	Dexamethasone	55	8153	0.52 (0.40–0.69)	<0.0001
	Famotidine	23	3197	0.59 (0.39–0.89)	0.0075
	Panvitan® powder for prescription *	9	1475	0.52 (0.28–0.99)	0.0293
	Acyclovir	7	1630	0.37 (0.18–0.76)	0.0017
	Pregabalin	5	1197	0.37 (0.16–0.86)	0.0070
	Diphenhydramine hydrochloride	3	957	0.30 (0.10–0.85)	0.0064
	Lenalidomide hydrate	1	2873	0.04 (0.01–0.20)	<0.0001
	Febuxostat	1	892	0.14 (0.03–0.67)	0.0005

* Panvitan® powder for prescription: Retinol palmitate, thiamine nitrate, riboflavin, pyridoxine hydrochloride, cyanocobalamin, ascorbic acid, ergocalciferol, tocopherol acetate, calcium pantothenate, nicotinamide and folic acid. [a] ATC: Anatomical Therapeutic Chemical. [b] ROR: Reporting odds ratio. [c] CI: Confidence interval.

4. Discussion

In the present study, 42 drugs were associated with OM. All the 42 drugs associated with OM has been reported that they are likely to cause OM in the package inserts of prescription drugs or textbook. The most frequently reported drugs associated with OM were tegafur/gimeracil/oteracil potassium, fluorouracil, cisplatin, everolimus, capecitabine, and oxaliplatin. These drugs are known to have a high incidence of OM in previous clinical trials [4,30–32]; hence, these antineoplastic drugs may have a high potential to induce OM. Cytotoxic antineoplastic drugs, such as alkylating drugs and antimetabolites, inhibit the growth of actively dividing cells with abundant blood flow [33]. Cells in the oral mucosa are believed to be susceptible to the cytotoxic effects of antineoplastic drugs because they are actively dividing. Molecularly targeted drugs, such as protein kinase inhibitors, are likely to have a lower incidence of OM than cytotoxic anticancer drugs, as they act only on specific target molecules in cancer cells [34]; however, everolimus and other mTOR inhibitors, which act on tumor growth, are associated with a higher incidence of OM than other molecularly targeted drugs [10].

In the present study, the median time to onset ranged from approximately 7.0 days to 23.0 days. This finding is consistent with that of previous studies, which showed that antineoplastic drug-induced OM occurs between a few days and 2–3 weeks after administration [35]. The Weibull distribution suggested that OM expression patterns may differ for each type of antineoplastic drug. Early failure was estimated for antimetabolites (e.g., tegafur/gimeracil/oteracil potassium), monoclonal antibodies, and antibody-drug conjugates (e.g., bevacizumab). Wear-out failure was estimated for alkylating drugs (e.g., melphalan). Antineoplastic drug-induced OM is caused via direct effects, such as destruction of the oral mucosa, inflammation, and secondary infections in the oral cavity associated with bone marrow suppression, including leukopenia. OM caused by secondary infections develops later than that caused by the direct action of antineoplastic drugs [36]. These findings explain why more than one drug exhibited wear-out failure among the alkylating drugs in this study. The Weibull distribution could be valuable in establishing the specific safety monitoring period for AEs based on expression patterns of OM. Therefore, OM attributed to antineoplastic drugs that exhibit wear-out failure of use may require longer-term monitoring than other antineoplastic drugs. However, the use of avelumab should be carefully considered owing to the lack of data (n = 2).

Hierarchical cluster analysis classified antineoplastic drugs into four clusters based on the presence or absence of disproportionality of OM-related AEs. Stomatitis was associated with all clusters; therefore, it was expected to be associated with all antineoplastic drugs. The third cluster, which included all drugs classified as cytotoxic antibiotics and related substances, was associated with pharyngeal ulceration and mouth ulceration; this cluster

also included dactinomycin, everolimus, and methotrexate. These drugs are known to be associated with mouth ulceration [6,37,38]. Therefore, the risk of mouth ulceration with these drugs needs to be carefully considered. The fourth cluster, which included protein kinase inhibitors such as afatinib, lapatinib, and dacomitinib, was associated with lip erosion, hemorrhagic stomatitis, and glossitis. The incidence of lip erosion and glossitis was less than 10% or unknown on the package inserts of these drugs. However, molecularly targeted drugs, such as protein kinase inhibitors, are known to induce aphthous OM, and aphthous OM localized in non-excursion and keratinized mucosal areas are typical because these areas can be difficult to stimulate physically [19,39]. Further investigations are needed to evaluate the correlation between protein kinase inhibitors and these AEs.

Twelve of the concomitantly administered drugs were inversely associated with antineoplastic drug-induced OM by all antineoplastic drugs. In clinical trials, dexamethasone [12], prednisolone [40], and methylprednisolone [41] were shown to prevent OM. Lenalidomide hydrate, a thalidomide analog, improves aphthous OM [42]. Considering other drugs, evidence from clinical trials is lacking; however, febuxostat was found to exert antioxidant and anti-inflammatory effects [43–45]. In a study using a rat model, pretreatment with febuxostat reduced parotid salivary gland injury induced by 5-fluorouracil through potent antioxidant effects and inhibition of interleukin (IL)-1β and tumor necrosis factor (TNF)-α activity [46]. Cytotoxic drugs directly inhibit DNA synthesis and cellular biochemical metabolic pathways, leading to the production of inflammatory cytokines such as reactive oxygen species and TNF-α, tissue damage in the oral mucosa, and induction of apoptosis [47]. These findings indicate that febuxostat might reduce OM by exerting antioxidant effects and inhibiting IL-1β and TNF-α. Moreover, antineoplastic-induced OM can occur via secondary infection due to bone marrow suppression. Sulfamethoxazole/trimethoprim [48] and voriconazole [49] exert preventive effects against infections; hence, these drugs may prevent secondary OM induced by antineoplastic drugs. In Japan, sodium gualenate hydrate is recommended as a prophylactic drug for OM [15]. However, in the current study, a combination of the drugs showed an association with OM, which could be attributed to the fact that these drugs were used for patients at high risk of OM, and the number of cases was higher than expected. Furthermore, some other drugs that lacked an inverse association with OM were found to afford notable preventative effects against OM [11]. Hence, drugs that did not exhibit disproportionality could be candidates for OM prevention. Herein, concomitantly administered drugs displaying an inverse association with antineoplastic drug-induced mucositis differed within the ATC classification. Accordingly, it is important to determine the prophylactic effect against antineoplastic-induced OM by drug or ATC classification. Recently, the pathobiology of mucositis has been explored, and potential druggable targets that inhibit mucositis have been identified [50]. Our findings on drugs that showed an inverse association with OM could provide insights for further basic research elucidating the mechanisms of action leading to drug repositioning. The findings of this study could serve as a guide when considering drugs that should be prioritized when validating their prophylactic effect against antineoplastic-induced OM.

This study had several limitations. First, because the JADER database is a spontaneous reporting database, it lacks denominator information, and the frequency of AEs cannot be calculated. Second, in studies that utilize spontaneous reporting databases for adverse drug reactions, such as JADER, mild and well-known adverse reactions are less likely to be reported, and severe adverse reactions are more frequently reported, which may result in reporting biases [51]. Third, the data retrieved from the JADER database included inadequate information, such as blank data and the start date of administration; therefore, these data were excluded from the analysis. Fourth, for recently launched drugs, the number of cases is limited but occasionally higher than expected owing to aggressive reporting, a phenomenon known as the Weber effect [52]. Fifth, it was not possible to eliminate the impact of concomitantly administered medications on our evaluation [53,54]. Reportedly, concomitant therapy of antineoplastic drugs is associated with a higher incidence of OM

than monotherapy [1,55]. In the current study, we did not investigate the incidence of OM by monotherapy and combination regimens. Therefore, the signal indicators observed in the current study must be interpreted carefully, considering the effects of concomitant use. Sixth, spontaneous reports may lack information on concomitant medications, especially in terms of common AEs [56]. Moreover, AEs will decrease if appropriate medical care is afforded in clinical settings, which may provide signals that oppose the pharmacological basis [57]. This may affect the signals detected with and without concomitant medication. Finally, only the JADER database was used in this study. AEs reported in the JADER and FDA Adverse Event Reporting System FAERS databases are known to differ [58]. Therefore, we hope that the gaps caused by these limitations will be addressed in future research using other methods, such as a combination of database-based studies of patients with certain adverse reactions.

5. Conclusions

We investigated the disproportionality of OM caused by antineoplastic drugs using the JADER database and potential concomitant drug treatment to prevent OM. In total, 42 drugs were associated with OM. The Weibull distribution showed a distinctive time-to-onset pattern depending on the type of antineoplastic drug administered, which could be valuable in monitoring OM. Cluster analyses classified antineoplastic drugs according to the typical symptoms of OM. These findings suggest that antineoplastic drug-induced OM should be monitored based on expression patterns. Considering the inverse association analysis, several concomitant drugs were expected to be the candidate drugs for preventing antineoplastic drug-induced OM. Additional investigations are required to validate the preventive mechanisms and clinical evaluation of OM.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/scipharm92020034/s1, Figure S1: Two-by-two contingency table for calculating the reporting odds ratio and 95% confidence interval of oral mucositis; Table S1: Definition of oral mucositis; Table S2: Characteristics of antineoplastic drugs-treated case population.

Author Contributions: Conceptualization, H.M. and H.T.; methodology, H.M. and H.T.; software, H.M.; validation, H.T., T.O. and H.M.; formal analysis, K.E. and H.M.; investigation, H.M.; resources, K.E. and H.M.; data curation, H.M; writing—original draft preparation, H.M.; writing—review and editing, H.T., T.O. and T.I.; visualization, H.M.; supervision, H.T. and H.M.; project administration, H.T. and H.M. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This was a database-related observational study with no direct access to any research subjects; thus, no ethical approval was sought. All results in this study were obtained from data from the JADER database. All data from JADER were fully anonymized by the relevant regulatory authorities prior to access.

Informed Consent Statement: Not applicable.

Data Availability Statement: The datasets generated and/or analyzed in the current study are available in the JADER database. (https://www.pmda.go.jp/safety/info-services/drugs/adr-info/suspected-adr/0004.html; accessed on 15 July 2022).

Conflicts of Interest: Hajime Matsuo is an employee in Daiichi Sankyo Co., Ltd. (Tokyo, Japan) and has received personal fees from it. Daiichi Sankyo Co., Ltd. had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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