

Survey and Exploratory Analysis of Preventive Medications for Antineoplastic Drug-Induced Oral Mucositis Using the Japanese Adverse Drug Event Report Database

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Abstract

Oral mucositis (OM) ranks among the most frequent side effects linked to cancer therapies. Research examining the risk factors for antineoplastic-induced OM and potential preventive strategies remains scarce. To address this, we performed a disproportionality analysis of antineoplastic drug-associated OM and investigated possible preventive agents using data from the Japanese Adverse Drug Event Report (JADER) database. According to JADER records spanning April 2004 to March 2022, antineoplastic agents were implicated in 210,822 adverse event reports, including 2,922 cases of OM. Forty-two drugs demonstrated a signal of association with OM. Application of the Weibull distribution revealed distinct time-to-onset profiles across antineoplastic drug classes. Cluster analysis grouped antineoplastic agents based on characteristic symptom profiles of OM. These results indicate that monitoring for antineoplastic-induced OM should account for distinct symptom expression patterns. Analysis of inverse associations identified several co-administered medications, such as lenalidomide hydrate and febuxostat, as potential candidates for preventing antineoplastic drug-induced OM. The co-administered drugs exhibiting inverse associations varied across Anatomical Therapeutic Chemical (ATC) categories. These observations may help prioritize agents for future clinical validation of their prophylactic efficacy against antineoplastic-induced OM.

Keywords: Oral mucositis (OM), Japanese adverse drug event report (JADER), Disproportionality analysis, Weibull distribution, Cluster analysis, Inverse association

Introduction

Oral mucositis (OM) is an inflammatory condition affecting the mucosal lining of the oral cavity and is among the most prevalent adverse events (AEs) associated with antineoplastic treatments [1-3]. It significantly impairs patients' quality of life and their

capacity to continue therapy. Core symptoms include oral pain, bleeding, xerostomia, erythema, mucosal swelling, trismus, speech difficulties, swallowing problems, and altered taste perception. In severe instances, intense pain can severely limit oral intake. The incidence of antineoplastic drug-induced OM differs markedly by agent. Reported frequencies include up to 65% for alkylating agents (e.g., cyclophosphamide), plant alkaloids and natural products (e.g., docetaxel), and cytotoxic antibiotics (e.g., doxorubicin) [4]; 14%–35% for antimetabolites (e.g., fluorouracil) [4]; 67% for everolimus [5]; 5%–33% for sorafenib [6]; 40.5% for bevacizumab [7]; and around 40% for platinum-based drugs [4]. Chemotherapy-related OM typically emerges

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3–4 days after administration, reaches peak severity at approximately 2 weeks, and largely resolves by 3 weeks [8, 9]. Onset timing for protein kinase inhibitors and other targeted therapies varies. Yet, mTOR inhibitors such as everolimus tend to cause OM within days, with a median onset of about 10 days and resolution within approximately 1 week [10]. These observations underscore the need to monitor antineoplastic-induced OM with attention to specific symptom timelines and patterns. Primary resources for OM management include drug package inserts and clinical trial data [11]. However, most existing reports [12, 13] focus on selected agents or rely on meta-analyses [14], leaving a gap in comprehensive data covering all antineoplastic drugs. No highly effective preventive medications for drug-induced OM have been established to date. In Japan, the Ministry of Health, Labor, and Welfare recommends agents such as sodium gualenate hydrate and sodium bicarbonate for prophylaxis [15], yet these lack targeted anti-mucositis activity. Recent meta-analyses of 10,514 participants across 131 trials identified several interventions—aloe vera, amifostine, cryotherapy, granulocyte-colony stimulating factor, intravenous glutamine, honey, keratinocyte growth factor, laser therapy, polymyxin/tobramycin/amphotericin pastilles or paste, and sucralfate—as providing notable preventive benefits against OM [11]. Additional reports describe remission of OM with herbal extracts used as mouthwashes or topical formulations containing benzocaine [16]. A multicenter phase II single-arm study (SWISH) in breast cancer patients on everolimus plus exemestane found that dexamethasone mouthwash lowered the rate of grade 2 or higher OM [12]. Nevertheless, such evidence is restricted to particular antineoplastic regimens and does not apply broadly. Reports of OM linked to newer agents, including molecular targeted therapies and immune checkpoint inhibitors, continue to rise [17–19]. Consequently, the development of broadly effective preventive options is urgently needed. Pharmacovigilance database studies are increasingly used globally to assess drug-AE relationships, characterize time-to-onset distributions, and explore drug repurposing opportunities [20]. The Japanese Adverse Drug Event Report (JADER) database, maintained by the Pharmaceuticals and Medical Devices Agency (PMDA), has proven valuable for examining drug-AE linkages [21, 22].

For optimal antineoplastic therapy, accurate assessment of OM risk per agent and identification of preventive options are essential. This study evaluated the disproportionality of antineoplastic drugs with OM and examined symptom expression patterns using the JADER database. Findings reinforce the need for antineoplastic-induced OM monitoring tailored to symptom profiles. We also screened for candidate preventive drugs, identifying several concomitant agents—including lenalidomide hydrate and febuxostat—as promising for reducing the risk of antineoplastic-induced OM. These results offer a foundation for selecting agents warranting further evaluation of prophylactic effects in patients receiving antineoplastic treatment.

Materials and Methods

Data sources

The JADER database, released by the PMDA, compiles spontaneous reports of adverse drug reactions. Reports are publicly downloadable, updated monthly, and available on the PMDA website (<http://www.pmda.go.jp/>; accessed on 15 July 2022). The database consists of four tables: patient demographics (demo), drug information (drug), adverse events (reac), and primary disease history (hist). Each entry links via a unique case identification number. Data downloaded on 15 July 2022 covered reports from April 2004 through March 2022. Drugs were categorized as suspected, concomitant, or interacting; all categories were included to assess relevance to OM comprehensively and to explore inverse associations with potential preventive agents. Duplicate drugs sharing the same case ID were removed. Adverse events in the “reac” table followed Preferred Terms from the Medical Dictionary for Regulatory Activities/Japan (MedDRA/J). Extraction used MedDRA/J version 25.1 (<https://www.jmo.pmrj.jp/>; accessed on 15 July 2022). Cases with repeated OM reports under the same ID were excluded.

Selection of antineoplastic drugs

Antineoplastic agents were selected based on ATC code L01 (<https://www.kegg.jp/brite/jp08303/A10BK02>; accessed on 15 July 2022). Indications were confirmed using relevant Standardized MedDRA Queries (SMQs) for malignancy-related conditions (SMQ 20000092), tumor markers (SMQ 20000094), specific malignant

tumors (SMQ 20000194), breast cancer (SMQ 20000198), ovarian cancer (SMQ 20000200), prostate cancer (SMQ 20000202), skin cancer (SMQ 20000204), uterine/fallopian tube cancer (SMQ 20000206), and malignant lymphomas (SMQ 20000215) [23].

Statistical analysis

The reporting odds ratio (ROR) quantified the association between antineoplastic drugs and OM using a 2×2 contingency table, a standard signal-detection method in pharmacovigilance databases [24]. To address zero-cell issues and small frequencies, the Haldane-Anscombe 1/2 correction was applied [25, 26]. A signal was considered present when the lower limit of the 95% confidence interval (CI) of the ROR exceeded 1, and Fisher's exact test yielded $P < 0.05$ [24]. Volcano plots were generated using $\ln(\text{ROR})$ and $-\log(p)$ to visualize associations [23, 27].

For time-to-onset analysis, only "suspected" drugs were used. Onset days were calculated as (onset date – first administration date) + 1. Values exceeding 365 days were capped at 365. The Weibull distribution's shape parameter β characterized onset patterns: $\beta \approx 1$ (constant

hazard), $\beta < 1$ (95% CI excluding 1) (early failure), and $\beta > 1$ (95% CI excluding 1) (wear-out failure) [28].

Hierarchical clustering grouped antineoplastic drugs based on their associated OM-related AEs. We included 42 drugs linked to OM and 11 OM-related AEs each reported in ≥ 10 cases. RORs were computed for each drug-AE pair, and a dendrogram was constructed using the Ward method with Euclidean distance based on the presence/absence of disproportionality signals [29].

For concomitant drugs, those with ≥ 100 total AE reports were analyzed. RORs and p-values (Fisher's exact test) were calculated and displayed in volcano plots. An inverse association was defined as an upper 95% CI limit of the ROR below 1 with $P < 0.05$ [24].

All analyses were conducted with JMP Pro 17 (SAS Institute Inc., Cary, NC, USA).

Results and Discussion

From April 2004 to March 2022, the JADER database contained 775,555 total reports. Antineoplastic drugs were associated with 210,822 AE cases, of which 2,922 involved OM (**Figure 1**).

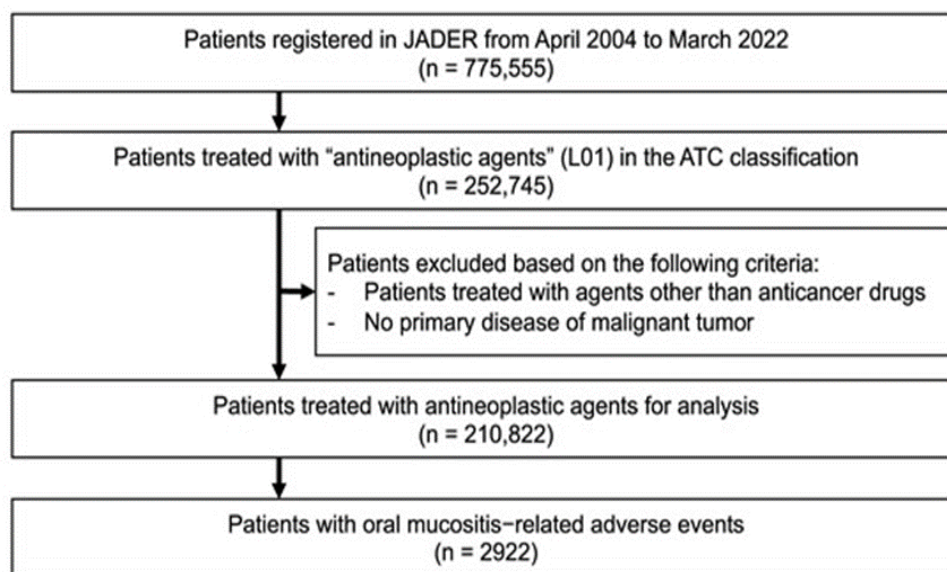


Figure 1. Flow diagram illustrating the selection of cases. JADER: Japanese Adverse Drug Event Report. ATC: Anatomical Therapeutic Chemical.

The sex distribution showed 40.3% females, 54.6% males, and 5.1% with unknown sex. In terms of age, the largest groups were patients aged 70–79 years (29.1%) and 60–69 years (28.0%). By ATC classification,

monoclonal antibodies and antibody-drug conjugates (L01F) represented the most common category (36.3%). Among patients who developed OM, the sex distribution was 47.1% female, 49.9% male, and 3.1% unknown or other. The predominant age groups were 60–69 years

(29.1%) and 70–79 years (28.9%). According to ATC classification, antimetabolites (L01B) were the most frequently involved (51.2%).

The case counts and corresponding ROR values for antineoplastic drug-associated OM are detailed in **Table 1**. **Figure 2** displays a volcano plot depicting the relationship between OM and various antineoplastic agents. As indicated in **Table 1** and **Figure 2**, a total of

42 drugs showed a positive association with OM. The agents most commonly linked to OM reports included tegafur/gimeracil/oteracil potassium (523 cases; 17.9%), fluorouracil (333 cases; 11.4%), cisplatin (305 cases; 10.4%), everolimus (264 cases; 9.0%), capecitabine (222 cases; 7.6%), and oxaliplatin (209 cases; 7.2%).

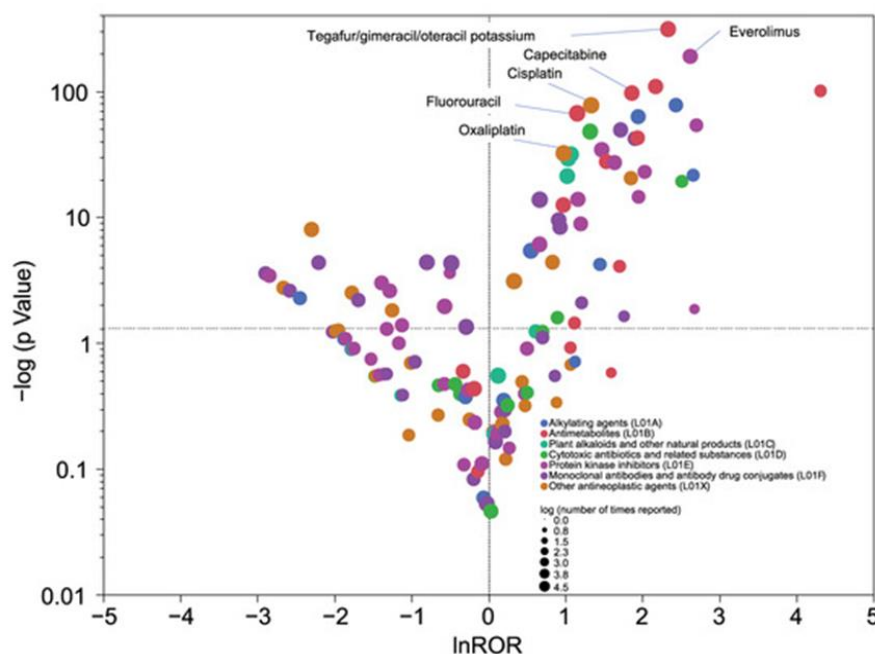


Figure 2. Antineoplastic medications showing signals for oral mucositis-associated adverse reactions.

The horizontal (x) axis displays the natural log of the reporting odds ratio (ln ROR), and the vertical (y) axis presents the negative base-10 logarithm of the p-value ($-\log(p\text{-value})$) obtained via Fisher's exact test. A horizontal dotted reference line indicates the $p = 0.05$ significance threshold. Point colors denote the ATC classification group, while point size is proportional to

the overall number of reports. Stronger positive shifts in ROR indicate a higher likelihood of the adverse reaction, and smaller p-values indicate greater statistical significance. Agents appearing in the upper right quadrant of the scatter plot are those with a notable link to oral mucositis-related AEs. AEs= adverse events; ROR= reporting odds ratio.

Table 1. Reports and reporting odds ratios for oral mucositis.

ATC ^a category	Drug	Cases (n)	Total reports (n)	ROR ^b (95% CI) ^c	P-value
Overall	Total	2922	210,822	—	—
Alkylating agents	Melphalan*	133	3370	6.99 (5.86–8.33)	< 0.0001
Alkylating agents	Busulfan*	118	1879	11.39 (9.43–13.75)	< 0.0001
Alkylating agents	Cyclophosphamide*	85	8307	1.73 (1.40–2.15)	< 0.0001
Alkylating agents	Thiotepa*	28	360	14.25 (9.71–20.92)	< 0.0001
Alkylating agents	Bendamustine	19	2665	1.22 (0.78–1.91)	0.4490

Alkylating agents	Ranimustine*	12	498	4.26 (2.43–7.47)	0.0001
Alkylating agents	Ifosfamide	9	1683	0.94 (0.50–1.78)	0.8740
Alkylating agents	Temozolomide	7	1678	0.74 (0.36–1.52)	0.4270
Alkylating agents	Streptozocin	2	136	1.12 (0.88–10.75)	0.1970
Alkylating agents	Dacarbazine	0	954	–	–
Alkylating agents	Carmustine	0	538	–	–
Alkylating agents	Nimustine	0	489	–	–
Alkylating agents	Larotrectinib	0	5	–	–
Alkylating agents	Carboquone	0	5	–	–
Antimetabolites	Tegafur/gimeracil/oteracil potassium*	523	9872	10.30 (9.39–11.31)	< 0.0001
Antimetabolites	Fluorouracil*	333	18,661	3.16 (2.83–3.54)	< 0.0001
Antimetabolites	Capecitabine*	222	6182	6.43 (5.61–7.38)	< 0.0001
Antimetabolites	Methotrexate*	198	4091	8.76 (7.57–10.13)	< 0.0001
Antimetabolites	Tegafur and uracil*	90	2285	6.93 (5.61–8.57)	< 0.0001
Antimetabolites	Fludarabine*	83	3110	4.63 (3.71–5.76)	< 0.0001
Antimetabolites	Cytarabine*	77	4971	2.65 (2.11–3.32)	< 0.0001
Antimetabolites	Pralatrexate*	73	238	74.60 (56.59–98.33)	< 0.0001
Antimetabolites	Gemcitabine	44	6889	1.08 (0.80–1.45)	0.6390
Antimetabolites	Pemetrexed	26	5290	0.83 (0.57–1.22)	0.3710
Antimetabolites	Azacitidine	11	2651	0.72 (0.40–1.28)	0.2560
Antimetabolites	Clofarabine*	9	295	5.49 (2.88–10.49)	0.0001
Antimetabolites	Mercaptopurine*	5	302	3.06 (1.32–7.11)	0.0370
Antimetabolites	Trifluridine and tipiracil hydrochloride	3	666	0.87 (0.30–2.49)	0.8040
Antimetabolites	Nelarabine	3	202	2.90 (1.02–8.35)	0.1230
Antimetabolites	Cladribine	1	171	1.45 (0.29–7.26)	1.0000
Antimetabolites	Tegafur	1	51	4.91 (0.97–24.93)	0.2650
Antimetabolites	Carmofur	0	8	–	–
Antimetabolites	Decitabine	0	1	–	–
Plant alkaloids and other natural products	Irinotecan*	173	10,253	2.92 (2.50–3.40)	< 0.0001
Plant alkaloids and other natural products	Docetaxel*	170	10,441	2.81 (2.41–3.28)	< 0.0001
Plant alkaloids and other natural products	Etoposide*	123	7583	2.78 (2.33–3.33)	< 0.0001
Plant alkaloids and other natural products	Paclitaxel	81	11,997	1.13 (0.91–1.41)	0.2840
Plant alkaloids and other natural products	Vincristine	47	7353	1.08 (0.81–1.43)	0.6490
Plant alkaloids and other natural products	Vinorelbine	13	1223	1.85 (1.08–3.16)	0.0592
Plant alkaloids and other natural products	Vinblastine	4	758	0.99 (0.39–2.49)	1.0000

Plant alkaloids and other natural products	Topotecan	0	482	–	–
Plant alkaloids and other natural products	Vindesine	0	482	–	–
Plant alkaloids and other natural products	Trabectedin	0	258	–	–
Plant alkaloids and other natural products	Cabazitaxel	0	2	–	–
Cytotoxic antibiotics and related substances	Doxorubicin*	187	8715	3.75 (3.23–4.34)	< 0.0001
Cytotoxic antibiotics and related substances	Dactinomycin*	27	398	12.31 (8.35–18.15)	< 0.0001
Cytotoxic antibiotics and related substances	Epirubicin	16	2658	1.03 (0.64–1.68)	0.9000
Cytotoxic antibiotics and related substances	Amrubicin	10	1364	1.28 (0.70–2.36)	0.4810
Cytotoxic antibiotics and related substances	Idarubicin	9	788	2.02 (1.06–3.83)	0.0602
Cytotoxic antibiotics and related substances	Mitoxantrone*	8	582	2.45 (1.24–4.82)	0.0262
Cytotoxic antibiotics and related substances	Pirarubicin	6	1550	0.70 (0.32–1.50)	0.4060
Cytotoxic antibiotics and related substances	Mitomycin	5	555	1.65 (0.71–3.83)	0.3970
Cytotoxic antibiotics and related substances	Daunorubicin	4	1150	0.65 (0.26–1.64)	0.3400
Cytotoxic antibiotics and related substances	Bleomycin	2	791	0.52 (0.15–1.81)	0.3480
Cytotoxic antibiotics and related substances	Aclarubicin	0	360	–	–
Protein kinase inhibitors	Everolimus*	264	3623	13.74 (12.08–15.63)	< 0.0001
Protein kinase inhibitors	Sunitinib*	111	4425	4.35 (3.60–5.27)	< 0.0001
Protein kinase inhibitors	Palbociclib*	73	2466	5.14 (4.07–6.50)	< 0.0001
Protein kinase inhibitors	Lapatinib*	70	865	14.86 (11.63–19.00)	< 0.0001
Protein kinase inhibitors	Sorafenib*	69	6031	1.94 (1.53–2.46)	< 0.0001
Protein kinase inhibitors	Erlotinib*	63	3378	3.20 (2.49–4.10)	< 0.0001
Protein kinase inhibitors	Afatinib*	44	1020	7.60 (5.62–10.28)	< 0.0001
Protein kinase inhibitors	Axitinib*	37	1919	3.31 (2.39–4.58)	< 0.0001
Protein kinase inhibitors	Temsirolimus*	29	726	7.03 (4.86–10.18)	< 0.0001
Protein kinase inhibitors	Gefitinib	21	3179	1.13 (0.74–1.72)	0.6440
Protein kinase inhibitors	Lenvatinib	18	2596	1.19 (0.75–1.88)	0.5230
Protein kinase inhibitors	Imatinib	16	4821	0.57 (0.35–0.92)	0.0114
Protein kinase inhibitors	Osimertinib	12	2699	0.77 (0.44–1.34)	0.3800
Protein kinase inhibitors	Regorafenib	11	2280	0.84 (0.47–1.50)	0.5860
Protein kinase inhibitors	Pazopanib	11	2079	0.92 (0.51–1.64)	0.7770
Protein kinase inhibitors	Cabozantinib	11	1164	1.65 (0.92–2.95)	0.1270
Protein kinase inhibitors	Ibrutinib	5	574	1.60 (0.69–3.70)	0.4050

Protein kinase inhibitors	Nilotinib	3	2316	0.25 (0.09–0.71)	0.0010
Protein kinase inhibitors	Dasatinib	3	2083	0.28 (0.10–0.79)	0.0026
Protein kinase inhibitors	Trametinib	3	583	1.00 (0.35–2.85)	1.0000
Protein kinase inhibitors	Crizotinib	2	1272	0.33 (0.09–1.12)	0.0421
Protein kinase inhibitors	Gilteritinib	2	734	0.56 (0.16–1.95)	0.3400
Protein kinase inhibitors	Dabrafenib	2	570	0.73 (0.21–2.52)	0.7810
Protein kinase inhibitors	Lorlatinib	2	317	1.31 (0.38–4.55)	0.7160
Protein kinase inhibitors	Dacomitinib*	2	30	14.51 (3.98–52.89)	0.0140
Protein kinase inhibitors	Nintedanib	1	918	0.27 (0.05–1.33)	0.0516
Protein kinase inhibitors	Ponatinib	1	793	0.31 (0.06–1.55)	0.1020
Protein kinase inhibitors	Cediranib	1	51	4.91 (0.97–24.93)	0.2650
Protein kinase inhibitors	Ruxolitinib	0	1417	–	–
Protein kinase inhibitors	Abemaciclib	0	624	–	–
Protein kinase inhibitors	Bosutinib	0	527	–	–
Protein kinase inhibitors	Alectinib	0	473	–	–
Protein kinase inhibitors	Ceritinib	0	379	–	–
Protein kinase inhibitors	Encorafenib	0	341	–	–
Protein kinase inhibitors	Binimetinib	0	319	–	–
Protein kinase inhibitors	Brigatinib	0	141	–	–
Protein kinase inhibitors	Vemurafenib	0	136	–	–
Protein kinase inhibitors	Entrectinib	0	123	–	–
Protein kinase inhibitors	Tepotinib	0	72	–	–
Protein kinase inhibitors	Vandetanib	0	71	–	–
Protein kinase inhibitors	Quizartinib	0	50	–	–
Protein kinase inhibitors	Capmatinib	0	22	–	–
Protein kinase inhibitors	Acalabrutinib	0	13	–	–
Protein kinase inhibitors	Selpercatinib	0	10	–	–
Protein kinase inhibitors	Pemigatinib	0	6	–	–
Monoclonal antibodies and ADCs	Bevacizumab*	169	14,834	1.95 (1.67–2.27)	< 0.0001
Monoclonal antibodies and ADCs	Cetuximab*	126	3973	5.56 (4.65–6.65)	< 0.0001
Monoclonal antibodies and ADCs	Panitumumab*	91	2387	6.70 (5.43–8.27)	< 0.0001
Monoclonal antibodies and ADCs	Trastuzumab*	64	4383	2.49 (1.94–3.19)	< 0.0001
Monoclonal antibodies and ADCs	Nivolumab	61	16,378	0.62 (0.48–0.80)	0.0001
Monoclonal antibodies and ADCs	Ramucirumab*	53	3562	2.54 (1.93–3.33)	< 0.0001
Monoclonal antibodies and ADCs	Rituximab	48	8240	0.98 (0.74–1.30)	0.8860

Monoclonal antibodies and ADCs	Pembrolizumab	43	9628	0.75 (0.55–1.01)	0.0465
Monoclonal antibodies and ADCs	Atezolizumab	27	4180	1.10 (0.75–1.60)	0.6870
Monoclonal antibodies and ADCs	Ipilimumab	20	7507	0.45 (0.29–0.70)	< 0.0001
Monoclonal antibodies and ADCs	Pertuzumab	11	1548	1.24 (0.69–2.21)	0.5100
Monoclonal antibodies and ADCs	Mogamulizumab	8	704	2.02 (1.03–3.97)	0.0797
Monoclonal antibodies and ADCs	Avelumab*	7	377	3.35 (1.63–6.91)	0.0084
Monoclonal antibodies and ADCs	Gemtuzumab ozogamicin	5	739	1.24 (0.54–2.87)	0.6360
Monoclonal antibodies and ADCs	Obinutuzumab	4	905	0.83 (0.33–2.08)	0.8270
Monoclonal antibodies and ADCs	Polatuzumab vedotin	3	527	1.10 (0.39–3.16)	1.0000
Monoclonal antibodies and ADCs	Necitumumab*	3	102	5.82 (2.00–16.91)	0.0240
Monoclonal antibodies and ADCs	Enfortumab vedotin	2	176	2.37 (0.68–8.26)	0.2860
Monoclonal antibodies and ADCs	Durvalumab	1	2244	0.11 (0.02–0.55)	< 0.0001
Monoclonal antibodies and ADCs	Daratumumab	1	1342	0.18 (0.04–0.92)	0.0067
Monoclonal antibodies and ADCs	Blinatumomab	1	644	0.39 (0.08–1.91)	0.1980
Monoclonal antibodies and ADCs	Inotuzumab ozogamicin	1	274	0.91 (0.18–4.51)	1.0000
Monoclonal antibodies and ADCs	Brentuximab vedotin	0	1493	–	–
Monoclonal antibodies and ADCs	Elotuzumab	0	1089	–	–
Monoclonal antibodies and ADCs	Trastuzumab emtansine	0	619	–	–
Monoclonal antibodies and ADCs	Trastuzumab deruxtecan	0	310	–	–
Monoclonal antibodies and ADCs	Isatuximab	0	251	–	–
Monoclonal antibodies and ADCs	Ofatumumab	0	107	–	–
Monoclonal antibodies and ADCs	Dinutuximab beta	0	17	–	–
Monoclonal antibodies and ADCs	Olaratumab	0	1	–	–
Other antineoplastics	Cisplatin*	305	14,308	3.79 (3.37–4.26)	< 0.0001
Other antineoplastics	Oxaliplatin*	209	13,643	2.65 (2.31–3.05)	< 0.0001
Other antineoplastics	Carboplatin*	118	14,283	1.39 (1.16–1.67)	0.0008

Other antineoplastics	Eribulin*	45	1238	6.36 (4.72–8.56)	< 0.0001
Other antineoplastics	Asparaginase	9	1319	1.20 (0.63–2.27)	0.5940
Other antineoplastics	Niraparib	6	701	1.55 (0.71–3.35)	0.3250
Other antineoplastics	Hydroxycarbamide	5	1165	0.78 (0.34–1.81)	0.5700
Other antineoplastics	Procarbazine	3	465	1.25 (0.44–3.58)	0.7610
Other antineoplastics	Tretinoin	3	362	1.61 (0.56–4.62)	0.4840
Other antineoplastics	Bortezomib	2	4088	0.10 (0.03–0.35)	< 0.0001
Other antineoplastics	Olaparib	2	1442	0.29 (0.08–0.99)	0.0156
Other antineoplastics	Mitotane	2	144	2.90 (0.83–10.14)	0.2150
Other antineoplastics	Ixazomib	1	1459	0.17 (0.03–0.84)	0.0032
Other antineoplastics	Estramustine	1	679	0.37 (0.07–1.81)	0.2040
Other antineoplastics	Arsenic trioxide	1	477	0.52 (0.10–2.59)	0.5420
Other antineoplastics	Vorinostat	1	103	2.42 (0.48–12.14)	0.4630
Other antineoplastics	Carfilzomib	0	1182	–	–
Other antineoplastics	Venetoclax	0	599	–	–
Other antineoplastics	Panobinostat	0	578	–	–
Other antineoplastics	Anagrelide	0	357	–	–
Other antineoplastics	Romidepsin	0	232	–	–
Other antineoplastics	Aminolevulinic acid	0	159	–	–
Other antineoplastics	Bexarotene	0	118	–	–
Other antineoplastics	Tisagenlecleucel	0	78	–	–
Other antineoplastics	Aflibercept	0	49	–	–
Other antineoplastics	Pentostatin	0	24	–	–
Other antineoplastics	Denileukin diftitox	0	20	–	–
Other antineoplastics	Porfimer sodium	0	16	–	–
Other antineoplastics	Veliparib	0	2	–	–
Other antineoplastics	Glasdegib	0	1	–	–

^a ATC: Anatomical Therapeutic Chemical. ^b ROR: Reporting odds ratio. ^c CI: Confidence interval. * Significant ROR (ROR $\geq$ 1, Lower limit of the 95% CI corresponding to the ROR $\geq$ 1, and P-value < 0.05).

Among the forty-two antineoplastic agents identified with signals for OM, 39 drugs possessing at least two valid records for both the initial administration date and the AE onset date were selected for the time-to-onset evaluation. **Figure 3** displays box-and-whisker plots summarizing the distribution of time until onset. **Table 2** lists the median onset times along with the Weibull-derived classification of OM onset patterns. Median times to OM development ranged from roughly 7.0 to

23.0 days across the agents. Based on Weibull analysis, the following drugs exhibited an early failure pattern: tegafur/gimeracil/oteracil potassium, fluorouracil, capecitabine, methotrexate, tegafur and uracil, pralatrexate, irinotecan, erlotinib, bevacizumab, trastuzumab, cisplatin, and eribulin. In contrast, melphalan, thiotepa, ranimustine, dactinomycin, palbociclib, and avelumab were classified as wear-out failure types.

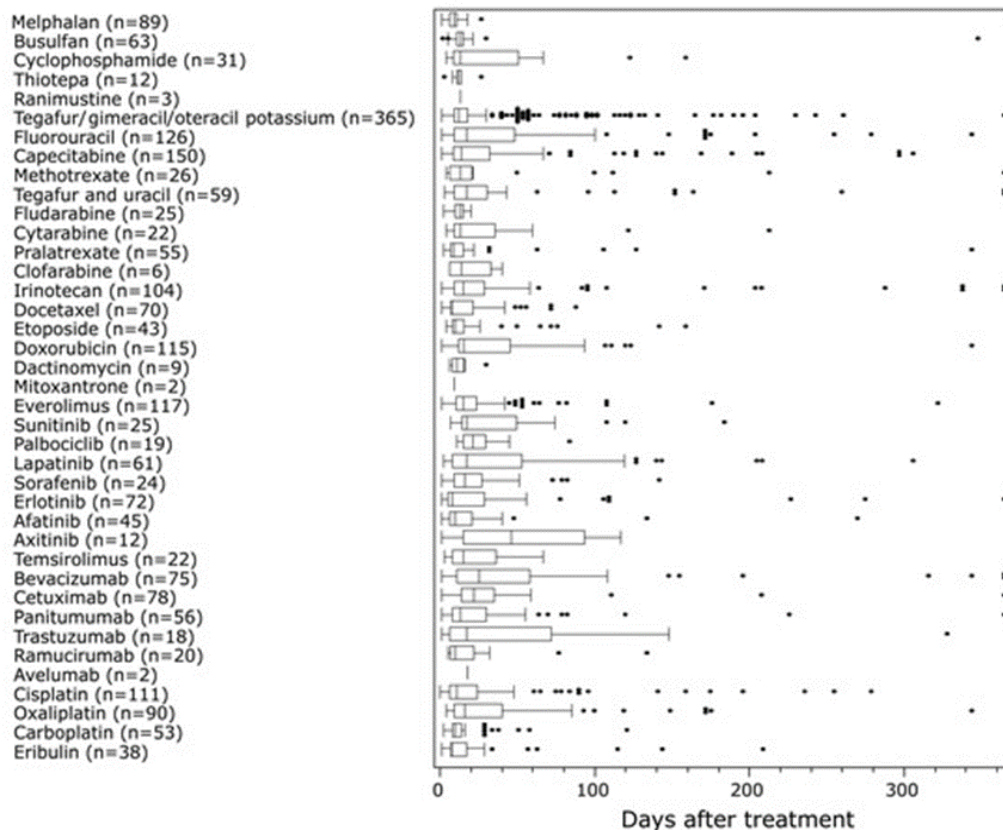


Figure 3. Box-and-whisker plot depicting the distribution of time until onset of oral mucositis linked to antineoplastic therapy.

Each box represents the interquartile range (25th to 75th percentiles) with the median marked inside. The whiskers indicate the highest and lowest values within 1.5 times the interquartile range. Any points falling outside this

range are plotted individually as outliers. All onset intervals longer than 365 days were capped at 365 days for the analysis.

Table 2. Median time to oral mucositis and Weibull distribution parameters for antineoplastic drugs.

ATC ^a category	Drug	Cases (n)	Median time (25–75%) days	Scale parameter α (95% CI)	Shape parameter β (95% CI ^b)	Failure pattern
Alkylating agents	Melphalan	89	9.0 (6.0–11.0)	9.90 (8.97–10.90)	2.28 (1.94–2.63)	Wear-out failure
Alkylating agents	Busulfan	63	13.0 (11.0–15.0)	17.85 (13.61–23.36)	0.98 (0.85–1.12)	Random failure
Alkylating agents	Cyclophosphamide	31	13.0 (9.0–53.0)	31.80 (21.47–46.21)	1.00 (0.76–1.28)	Random failure
Alkylating agents	Thiotepe	12	11.5 (10.25–14.0)	13.79 (10.45–17.96)	2.37 (1.49–3.40)	Wear-out failure
Alkylating agents	Ranimustine	3	13.0 (8.0–13.0)	12.26 (9.19–16.31)	6.58 (1.91–16.24)	Wear-out failure
Antimetabolites	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
Antimetabolites	Fluorouracil	126	18.0 (9.0–49.0)	37.45 (30.23–46.16)	0.88 (0.77–0.996)	Early failure

Antimetabolites	Capecitabine	150	14.0 (8.75–32.25)	30.66 (25.01–37.43)	0.85 (0.76–0.95)	Early failure
Antimetabolites	Methotrexate	26	13.0 (6.0–20.25)	30.24 (16.49–53.99)	0.71 (0.53–0.91)	Early failure
Antimetabolites	Tegafur + uracil	59	17.0 (9.0–32.0)	39.45 (27.50–55.92)	0.78 (0.64–0.92)	Early failure
Antimetabolites	Fludarabine	25	13.0 (10.0–15.0)	17.12 (11.86–24.45)	1.18 (0.90–1.48)	Random failure
Antimetabolites	Cytarabine	22	12.5 (9.0–33.75)	30.49 (17.99–50.36)	0.90 (0.65–1.17)	Random failure
Antimetabolites	Pralatrexate	55	8.0 (6.0–15.0)	17.67 (12.39–24.99)	0.81 (0.68–0.95)	Early failure
Antimetabolites	Clofarabine	6	20.0 (6.0–65.5)	36.54 (11.54–108.38)	0.89 (0.44–1.50)	Random failure
Plant alkaloids	Irinotecan	104	15.0 (9.0–29.0)	33.08 (25.18–43.18)	0.76 (0.67–0.87)	Early failure
Plant alkaloids	Docetaxel	70	8.0 (7.0–21.25)	17.06 (13.48–21.42)	1.09 (0.91–1.28)	Random failure
Plant alkaloids	Etoposide	43	10.0 (8.0–15.0)	21.83 (15.36–30.66)	0.94 (0.75–1.14)	Random failure
Cytotoxic antibiotics	Doxorubicin	115	16.0 (12.0–47.0)	32.26 (26.69–38.83)	1.04 (0.91–1.18)	Random failure
Cytotoxic antibiotics	Dactinomycin	9	9.0 (8.0–15.5)	14.27 (9.53–20.89)	1.95 (1.13–2.95)	Wear-out failure
Cytotoxic antibiotics	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	Everolimus	117	15.0 (10.0–23.5)	25.11 (20.75–30.28)	1.02 (0.90–1.15)	Random failure
Protein kinase inhibitors	Sunitinib	25	18.0 (14.5–57.0)	42.33 (27.80–63.05)	1.05 (0.77–1.38)	Random failure
Protein kinase inhibitors	Palbociclib	19	22.0 (15.0–30.0)	30.72 (22.34–41.57)	1.61 (1.13–2.15)	Wear-out failure
Protein kinase inhibitors	Lapatinib	61	17.0 (8.0–51.5)	38.23 (27.62–52.30)	0.85 (0.70–1.01)	Random failure
Protein kinase inhibitors	Sorafenib	24	15.5 (9.25–26.0)	28.34 (18.00–43.63)	0.99 (0.72–1.30)	Random failure
Protein kinase inhibitors	Erlotinib	72	8.0 (5.25–28.75)	23.42 (16.57–32.77)	0.73 (0.61–0.85)	Early failure
Protein kinase inhibitors	Afatinib	45	9.0 (6.0–20.5)	19.23 (13.23–27.66)	0.86 (0.70–1.02)	Random failure
Protein kinase inhibitors	Axitinib	12	53.0 (15.75–92.75)	57.70 (32.54–99.11)	1.18 (0.69–1.83)	Random failure
Protein kinase inhibitors	Temsirolimus	22	15.0 (7.75–36.0)	24.73 (16.92–35.38)	1.25 (0.88–1.70)	Random failure
Monoclonal antibodies	Bevacizumab	75	23.0 (11.0–58.0)	47.36 (35.01–63.47)	0.82 (0.69–0.96)	Early failure
Monoclonal antibodies	Cetuximab	78	22.0 (13.75–35.0)	30.93 (24.42–38.99)	1.02 (0.87–1.17)	Random failure
Monoclonal antibodies	Panitumumab	56	13.5 (8.25–31.5)	30.16 (21.66–41.59)	0.87 (0.72–1.02)	Random failure
Monoclonal antibodies	Trastuzumab	18	19.5 (6.5–89.25)	51.66 (23.62–107.87)	0.68 (0.46–0.94)	Early failure

Monoclonal antibodies	Ramucirumab	20	10.0 (7.0–22.0)	20.85 (12.30–34.46)	0.94 (0.67–1.24)	Random failure
Monoclonal antibodies	Avelumab	2	16.5 (15.0–18.0)	17.19 (14.06–21.22)	13.16 (2.88–35.52)	Wear-out failure
Other antineoplastics	Cisplatin	110	11.0 (6.0–26.25)	25.06 (19.23–32.46)	0.76 (0.67–0.87)	Early failure
Other antineoplastics	Oxaliplatin	90	16.0 (9.0–39.25)	33.58 (26.38–42.47)	0.93 (0.80–1.07)	Random failure
Other antineoplastics	Carboplatin	53	10.0 (8.0–13.5)	16.32 (12.57–21.02)	1.13 (0.93–1.34)	Random failure
Other antineoplastics	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 shows the results of hierarchical cluster analysis grouping antineoplastic agents according to the presence or absence of disproportionality signals for various OM-related adverse events. The resulting dendrogram separated the drugs into four distinct clusters. Every cluster demonstrated an association with stomatitis. Cluster 1 primarily contained fluorouracil along with several other agents, while Cluster 2 included docetaxel

and related drugs. Within the alkylating agents, cyclophosphamide belonged to Cluster 1, whereas the remaining alkylating agents fell into Cluster 2. All cytotoxic antibiotics and related substances were grouped in Cluster 3. These first three clusters were additionally linked to pharyngeal ulceration and mouth ulceration. Cluster 4 consisted mainly of protein kinase inhibitors (such as afatinib) and was characterized by associations with lip erosion, hemorrhagic stomatitis, and glossitis.

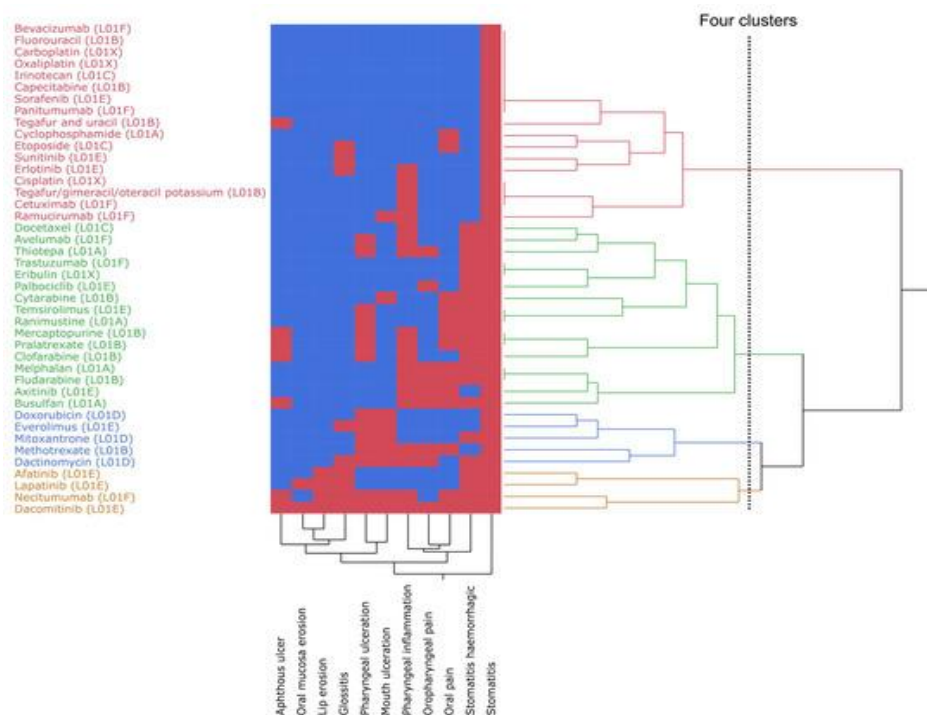


Figure 4. Grouping of oral mucositis-related adverse events through hierarchical cluster analysis.

The dendrogram illustrates linkages among 11 different OM-related AEs. The dashed line marks the boundaries between clusters. The heatmap indicates whether a

disproportionality signal was present or absent for each AE. Red denotes “present,” and blue denotes “absent.” AEs, adverse events.

Results concerning co-administered medications that displayed an inverse relationship with antineoplastic drug-induced OM are presented in **Table 3**. Twelve such drug combinations demonstrated inverse associations across all antineoplastic-induced OM cases. **Figure 5a** displays a volcano plot examining the relationship between these concomitant drugs and antineoplastic-induced OM. Agents including dexamethasone, prednisolone, methylprednisolone, sulfamethoxazole/trimethoprim, voriconazole, febuxostat, and lenalidomide hydrate showed inverse associations. Notably, sodium guaienate hydrate, a medication commonly recommended for OM prevention or treatment, did not exhibit any inverse association.

Figures 5b–5h provide volcano plots stratified by ATC categories, highlighting the links between concomitant therapies and OM induced by specific antineoplastic drug classes. Lenalidomide hydrate demonstrated an inverse association with OM caused by monoclonal antibodies, antibody-drug conjugates, and other antineoplastic agents. Febuxostat was inversely associated with OM triggered by antimetabolites and additional antineoplastic drugs. Dexamethasone showed an inverse association specifically with OM, compared with other antineoplastic agents. At the same time, prednisolone exhibited inverse associations with OM induced by alkylating agents, plant alkaloids and natural products, as well as cytotoxic antibiotics and related substances.

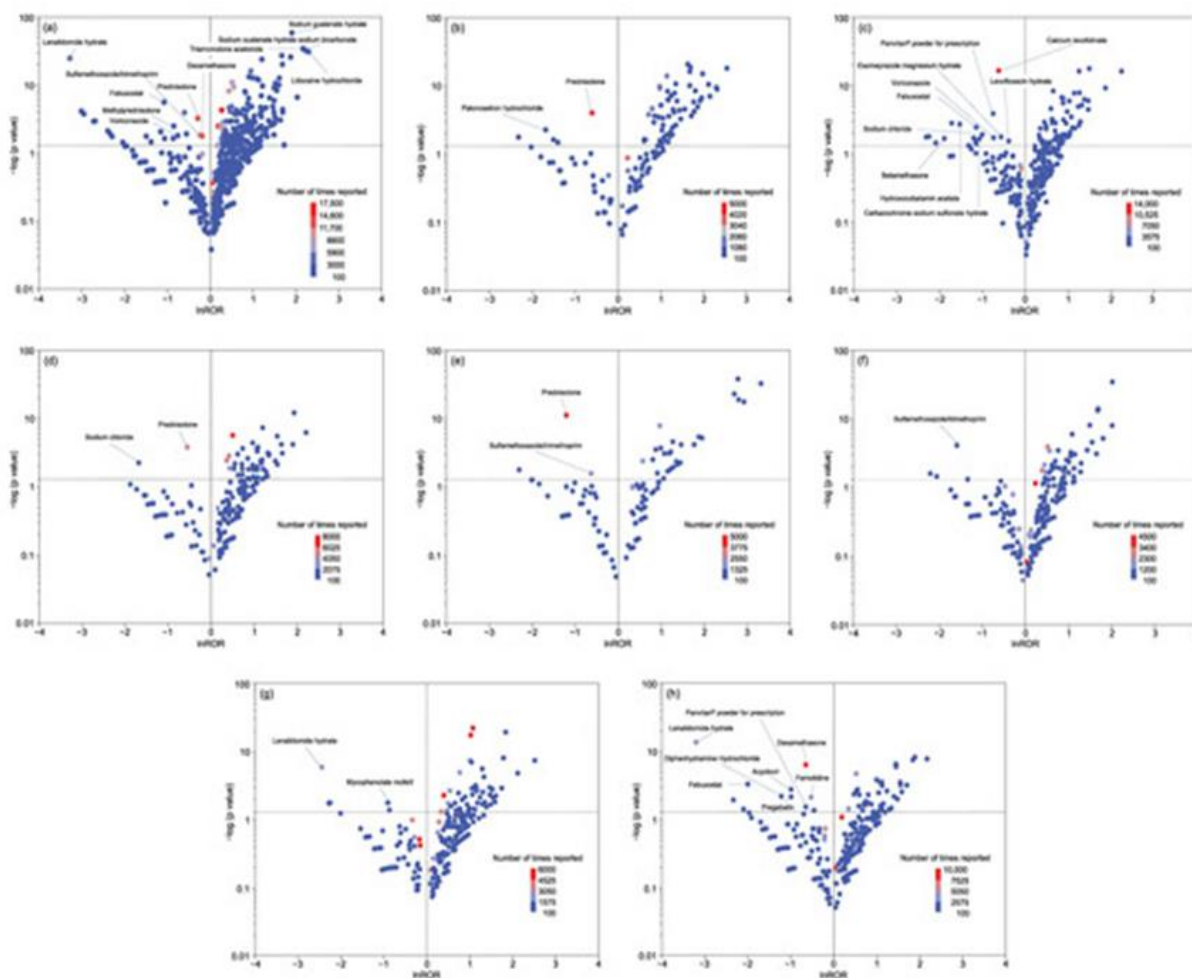


Figure 5. Concomitant agents and their relationship to oral mucositis-related adverse reactions when used together with antineoplastic treatments.

The panels illustrate combinations with (a) the full set of antineoplastic drugs, (b) alkylating agents, (c) antimetabolites, (d) plant alkaloids plus other natural products, (e) cytotoxic antibiotics and related

compounds, (f) protein kinase inhibitors, (g) monoclonal antibodies and antibody-drug conjugates, and (h) miscellaneous antineoplastic drugs. The x-axis indicates the natural log of the reporting odds ratios (ln ROR), and the y-axis shows the base-10 negative logarithm of the p-value ($-\log(p\text{-value})$) from Fisher's exact test. A horizontal dotted line marks the $p = 0.05$ level. Colors of the data points reflect the overall report volume. Stronger

negative shifts in ROR are associated with a lower likelihood of adverse reactions, while smaller p-values indicate greater statistical significance. Agents located in the upper-left quadrant of these plots represent concomitant drugs that are less commonly associated with oral mucositis-related AEs. AEs, adverse events; ROR, reporting odds ratio.

Table 3. Report counts and reporting odds ratios for concomitant medications associated with reduced oral mucositis risk.

ATC ^a category	Concomitant Drug	Cases (n)	Total reports (n)	ROR ^b (95% CI ^c)	P-value
All antineoplastic agents	Dexamethasone	169	14,512	0.83 (0.71–0.97)	0.0168
All antineoplastic agents	Prednisolone	142	13,407	0.75 (0.63–0.89)	0.0006
All antineoplastic agents	Sulfamethoxazole/trimethoprim	102	9295	0.79 (0.64–0.96)	0.0142
All antineoplastic agents	Esomeprazole magnesium hydrate	35	4585	0.55 (0.39–0.77)	0.0001
All antineoplastic agents	Mycophenolate mofetil	17	2170	0.58 (0.36–0.92)	0.0125
All antineoplastic agents	Febuxostat	13	2798	0.34 (0.20–0.58)	<0.0001
All antineoplastic agents	Methylprednisolone	9	1579	0.43 (0.23–0.81)	0.0033
All antineoplastic agents	Voriconazole	8	1285	0.47 (0.24–0.93)	0.0159
All antineoplastic agents	Edoxaban tosilate hydrate	5	928	0.42 (0.18–0.98)	0.0231
All antineoplastic agents	Azilsartan	3	789	0.32 (0.11–0.90)	0.0089
All antineoplastic agents	Basiliximab	3	720	0.35 (0.12–0.99)	0.0233
All antineoplastic agents	Lenalidomide hydrate	2	4602	0.04 (0.01–0.13)	<0.0001
Alkylating agents	Prednisolone	44	4536	0.55 (0.40–0.76)	0.0001
Alkylating agents	Palonosetron hydrochloride	1	490	0.19 (0.04–0.93)	0.0055
Antimetabolites	Calcium levofolinate	187	12,629	0.47 (0.46–0.63)	<0.0001
Antimetabolites	Levofloxacin hydrate	30	1782	0.68 (0.47–0.98)	0.0296
Antimetabolites	Panvitan® powder for prescription*	21	1787	0.47 (0.31–0.73)	0.0001
Antimetabolites	Betamethasone	17	389	0.15 (0.03–0.76)	0.0211
Antimetabolites	Esomeprazole magnesium hydrate	15	1085	0.57 (0.34–0.94)	0.0173
Antimetabolites	Voriconazole	8	705	0.48 (0.24–0.94)	0.0194
Antimetabolites	Febuxostat	4	557	0.32 (0.13–0.81)	0.0036
Antimetabolites	Sodium chloride	4	486	0.37 (0.14–0.93)	0.0122
Antimetabolites	Carbazochrome sodium sulfonate hydrate	3	402	0.34 (0.12–0.99)	0.0221
Antimetabolites	Hydroxocobalamin acetate	2	453	0.22 (0.06–0.76)	0.0020

Plant alkaloids	Prednisolone	43	5835	0.57 (0.42–0.78)	0.0002
Plant alkaloids	Sodium chloride	1	646	0.19 (0.04–0.92)	0.0059
Cytotoxic antibiotics	Prednisolone	26	4636	0.30 (0.20–0.45)	<0.0001
Cytotoxic antibiotics	Sulfamethoxazole/trimethoprim	11	1339	0.53 (0.30–0.97)	0.0270
Protein kinase inhibitors	Sulfamethoxazole/trimethoprim	3	1162	0.20 (0.07–0.58)	<0.0001
Monoclonal antibodies and ADCs	Lenalidomide hydrate	1	1862	0.09 (0.02–0.43)	<0.0001
Monoclonal antibodies and ADCs	Mycophenolate mofetil	5	1485	0.40 (0.17–0.94)	0.0170
Other antineoplastic agents	Dexamethasone	55	8153	0.52 (0.40–0.69)	<0.0001
Other antineoplastic agents	Famotidine	23	3197	0.59 (0.39–0.89)	0.0075
Other antineoplastic agents	Panvitan® powder for prescription*	9	1475	0.52 (0.28–0.99)	0.0293
Other antineoplastic agents	Acyclovir	7	1630	0.37 (0.18–0.76)	0.0017
Other antineoplastic agents	Pregabalin	5	1197	0.37 (0.16–0.86)	0.0070
Other antineoplastic agents	Diphenhydramine hydrochloride	3	957	0.30 (0.10–0.85)	0.0064
Other antineoplastic agents	Lenalidomide hydrate	1	2873	0.04 (0.01–0.20)	<0.0001
Other antineoplastic agents	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.

This study identified 42 drugs linked to oral mucositis (OM). All of these agents have previously been documented as capable of inducing OM in their respective prescription drug package inserts or in standard medical textbooks. The drugs most commonly implicated were tegafur/gimeracil/oteracil potassium, fluorouracil, cisplatin, everolimus, capecitabine, and oxaliplatin. These agents are recognized for their elevated rates of OM in earlier clinical trials [4, 30-32] and therefore appear to pose a substantial risk of triggering this adverse effect. Cytotoxic antineoplastic agents, including alkylating agents and antimetabolites, suppress the proliferation of rapidly dividing cells that receive a rich blood supply [33]. Because epithelial cells in the oral mucosa divide actively, they are particularly vulnerable to the cytotoxic impact of these drugs. In contrast, molecularly targeted therapies, such as protein kinase inhibitors, generally exhibit a lower frequency of OM than conventional cytotoxic chemotherapies, as their action is more selective for specific molecules in tumor

cells [34]. Nevertheless, mTOR inhibitors like everolimus have a higher incidence of OM than other classes [10].

In the current analysis, the median time to OM onset spanned roughly 7.0 to 23.0 days. This timeframe aligns with prior research indicating that antineoplastic-induced OM typically emerges within 2–3 weeks of treatment initiation [35]. Application of the Weibull distribution revealed that the pattern of OM manifestation can vary across specific antineoplastic drug categories. Early failure patterns were observed with antimetabolites (e.g., tegafur/gimeracil/oteracil potassium), monoclonal antibodies, and antibody-drug conjugates (e.g., bevacizumab). Wear-out failure patterns were identified for alkylating agents (for instance, melphalan). Antineoplastic drug-induced OM arises from direct mucosal damage, inflammatory responses, and secondary infections associated with bone marrow suppression (including leukopenia). Secondary infection-related OM tends to appear later than OM resulting from

the direct cytotoxic action of the drugs [36]. These mechanisms likely account for the wear-out failure pattern seen with several alkylating agents in this dataset. The Weibull approach may prove useful for defining appropriate safety monitoring windows tailored to the temporal expression profile of OM. Consequently, antineoplastic drugs exhibiting wear-out failure may necessitate extended monitoring periods compared with other agents. Caution is advised with avelumab, however, due to the very small number of cases available ($n = 2$). Hierarchical clustering grouped antineoplastic drugs into 4 clusters based on whether they showed disproportionate reporting of OM-related adverse events. Stomatitis was linked to every cluster, indicating a broad association across all antineoplastic agents. The third cluster, encompassing all cytotoxic antibiotics and related substances, showed associations with pharyngeal ulceration and mouth ulceration; this group also contained dactinomycin, everolimus, and methotrexate. These medications are already known to be connected with mouth ulceration [6, 37, 38], underscoring the need for heightened attention to this risk. The fourth cluster, which included protein kinase inhibitors such as afatinib, lapatinib, and dacomitinib, was associated with lip erosion, hemorrhagic stomatitis, and glossitis. Although package inserts report incidence rates below 10% or list these events as unknown for these drugs, molecularly targeted agents, such as protein kinase inhibitors, are recognized for inducing aphthous-type OM. Such lesions characteristically occur in non-traumatized, keratinized mucosal regions that are less subject to mechanical irritation [19, 39]. Additional studies are warranted to clarify the relationship between protein kinase inhibitors and these specific adverse events.

Twelve concomitantly administered drugs demonstrated an inverse association with antineoplastic drug-induced OM across all such agents. Clinical trials have established the protective role of dexamethasone [12], prednisolone [40], and methylprednisolone [41] against OM. Lenalidomide hydrate, a thalidomide derivative, has been shown to alleviate aphthous OM [42]. For other agents, direct clinical trial evidence is limited, yet febxostat possesses documented antioxidant and anti-inflammatory properties [43-45]. In a rat model, pre-treatment with febxostat attenuated 5-fluorouracil-induced parotid gland damage via strong antioxidant activity and suppression of interleukin (IL)-1 β and tumor necrosis factor (TNF)- α [46]. Cytotoxic drugs trigger the release of inflammatory cytokines—including reactive

oxygen species and TNF- α —leading to mucosal tissue injury and apoptosis [47]. These observations suggest that febxostat may mitigate OM through antioxidant mechanisms and cytokine inhibition.

Additionally, antineoplastic-induced OM can develop secondarily due to immunosuppression-related infections; sulfamethoxazole/trimethoprim [48] and voriconazole [49] offer protection against such infections and may therefore help prevent secondary OM. In Japan, sodium gualenate hydrate is recommended for OM prophylaxis [15]. In the present analysis, however, its combined use was positively associated with OM, possibly because it is preferentially administered to high-risk patients, leading to more reports than anticipated. Certain other drugs lacking an inverse signal have also demonstrated notable preventive potential against OM in prior work [11]. Thus, agents without disproportionality signals represent promising candidates for further prevention research. The concomitantly administered drugs showing inverse associations varied across Anatomical Therapeutic Chemical (ATC) classifications, highlighting the importance of evaluating prophylactic effects at both the individual drug and class levels. Recent advances in understanding mucositis pathobiology have uncovered potential therapeutic targets [50]. The drugs identified here with inverse associations may inform future mechanistic studies and support drug repositioning efforts. Overall, these results can help prioritize agents for validation of their efficacy in preventing antineoplastic-induced OM.

Several limitations should be acknowledged. First, the JADER database is a spontaneous reporting system without denominator data, which prevents the calculation of actual adverse event frequencies. Second, spontaneous reporting databases such as JADER tend to under-report mild or well-known reactions while over-reporting severe ones, introducing reporting bias [51]. Third, the retrieved data contained missing information (e.g., blank fields and administration start dates), which led to exclusion of those records. Fourth, recently approved drugs may show inflated reporting due to the Weber effect [52]. Fifth, the influence of concomitant medications could not be fully excluded [53, 54]. Combination antineoplastic therapy is known to increase OM incidence relative to monotherapy [1, 55], yet the present study did not differentiate between monotherapy and combination regimens. Therefore, the observed signals require cautious interpretation in light of potential polypharmacy effects. Sixth, spontaneous reports

frequently lack complete details on concomitant drugs, particularly for common adverse events [56].

Furthermore, effective clinical management can reduce adverse events, sometimes producing signals that contradict expected pharmacology [57], which may influence results with or without concomitant medications. Finally, the analysis relied solely on the JADER database. Reporting patterns in JADER and the FDA Adverse Event Reporting System (FAERS) are known to differ [58]. Future studies employing complementary approaches, such as targeted patient cohort analyses, are encouraged to address these gaps.

Conclusion

This investigation examined the disproportionality signals for oral mucositis associated with antineoplastic drugs in the JADER database and explored potential concomitant medications that may prevent OM. A total of 42 drugs were found to be associated with OM. The Weibull distribution analysis revealed distinct time-to-onset profiles by antineoplastic drug type, which can aid targeted monitoring of OM. Cluster analysis grouped the drugs by OM symptom characteristics. These results indicate that monitoring for antineoplastic drug-induced OM should be tailored to the specific temporal and symptomatic patterns observed. The inverse association analysis identified several concomitant drugs as promising candidates for preventing antineoplastic-induced OM. Further research is necessary to confirm their mechanisms of action and to evaluate their efficacy in clinical trials.

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Ethics Statement: None

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