Original Article

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Real-world use of non-oral administration of oral anticancer agents *via* the simple suspension method in Japanese patients with cancer: A nationwide claims-based analysis

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SUMMARY: The enteral administration of drugs as suspensions is a potential alternative route for patients with dysphagia. The simple suspension method is commonly used in Japan; however, nationwide data are lacking. This study aimed to investigate the real-world use and potential impact of oral anticancer agent (OAA) suspensions in patients with dysphagia in Japan. A large Japanese administrative claims database was used in this retrospective study (April 2014 to August 2023). Patients with cancer who had nasogastric, gastrostomy, or jejunostomy tubes and received OAAs during non-oral intake periods were included. These periods were defined using procedural codes, and it was assumed that the prescribed drugs were suspended. Three frequently used drugs (temozolomide, lenvatinib, and osimertinib) were analyzed. Patients were divided into suspension and non-suspension groups using propensity score matching, and overall survival (OS) was compared using the Kaplan–Meier method. Among 25,252 patients with feeding tubes, 126 received OAAs during the non-oral period. The median age was 76 years, and 62% had gastrostomy tubes. Temozolomide was the most common drug suspension, followed by lenvatinib and osimertinib. No significant difference in OS was observed between the temozolomide and lenvatinib groups. However, OS of the osimertinib suspension group was shorter than that of the non-suspension group (p = 0.047). This large-scale study of OAA suspensions in Japan suggests that drug suspensions may support continued anticancer treatment in patients with dysphagia. However, drug stability and exposure risks should be considered. Further evidence and more specific guidelines are required to ensure safe and effective use.

Keywords: anticancer drug suspensions, enteral administration, dysphagia, Japanese cohort

1. Introduction

The development and widespread use of oral anticancer agents (OAAs) in recent years have led to an increase in outpatient cancer treatment. This shift offers advantages, such as reduced hospital visits and decreased physical and psychological burden, thereby maintaining the patients' quality of life. However, ensuring patient adherence is crucial for maximizing the efficacy of oral therapies (*1*). Older individuals and patients with advanced cancer often experience dysphagia, making oral administration challenging with potential treatment interruptions. In Japan, the clinical burden of dysphagia has been increasing; for example, the incidence of aspiration pneumonia, which is a major complication of dysphagia, rose by 53.7% between 2005 and 2019, with the majority of cases observed in individuals aged 70 years or older (*2*). Alternatively, OAA suspensions can be administered *via* feeding tubes.

In Japan, the simple suspension method (SSM), developed in 1997 and officially recognized in 2020, is now reimbursed under the Japanese medical insurance system (*3*). SSM involves suspension of tablets and capsules in warm water without physical crushing, further improving the stability and reducing the risk of exposure for healthcare providers and caregivers. However, data on the feasibility, stability, and pharmacokinetics of individual OAAs in suspension remain limited, highlighting the need for evidence-based, safe, and effective use (*3*). Treatment decisions should consider the therapeutic goals (*e.g.*, adjuvant or palliative chemotherapy), patient condition, available alternatives, and patient and family preferences. Pharmacists and other healthcare professionals should provide support from a pharmaceutical perspective, including safety evaluations and pharmacokinetics.

Japan has a rapidly aging society, with a growing population of individuals aged ≥ 85.0 years. This

population is experiencing increased rates of age-related comorbidities, including stroke, dementia, and Parkinson's disease, which impair swallowing and increase the risk of dysphagia (*4,5*). In these patients, a low prognostic nutritional index is associated with increased mortality, and many of them also have cancer (*6*). The number of older patients with cancer and dysphagia is expected to increase, necessitating systems to support cases where oral drug administration is challenging. However, the real-world use of OAA suspensions in Japan remains unexplored. Understanding the current clinical practices is critical for optimizing decisions regarding drug selection and administration, formulation strategies, guideline development, and patient support systems.

This study aimed to investigate the real-world use of OAA suspensions in patients unable to receive oral medications in clinical settings. This method is considered off-label, and we assumed that it would be rarely practiced. Therefore, we used a large Japanese administrative claims database to clarify its real-world use, patient characteristics, and potential impact on outcomes.

2. Materials and Methods

2.1. Study design and data source

This retrospective study examined the real-world use of OAA suspensions in Japan. Data were obtained from the DeSC, a commercial administrative claims repository provided by DeSC Healthcare, Inc. (Tokyo, Japan; *https://desc-hc.co.jp/*). As of October 2022, the database contained the information of approximately 12 million insured individuals. It integrates information from three major health insurance schemes under Japan's mandatory universal healthcare system: Kenpo (for employees of large corporations), Kokuho (for non-employees, retirees, and their dependents), and the Koki Koreisha Iryo Seido (for individuals aged ≥ 75.0 years). Collectively, these schemes cover 9.8% of the Japanese population and offer a comprehensive nationwide overview of healthcare utilization.

2.2. Study population

Of the 1,838,927 patients with a confirmed diagnosis of cancer (based on International Statistical Classification of Diseases and Related Health Problems [ICD-10] codes starting with "C," excluding suspected cases) between April 2014 and August 2023, we included those who underwent nasogastric tube (NGT), gastrostomy, or jejunostomy tube placement and were prescribed OAAs during the non-oral intake period. Patients who were prescribed orally disintegrating tablets, dispersible tablets, or powders were excluded.

The index date was defined as the first day on which an OAA suspension was administered. As this study aimed to describe the status of suspension administration rather than conduct a longitudinal follow-up, treatment progress or prognosis following suspension administration were not assessed. Patients with data available for < 30 days before the index date were excluded (*7,8*).

We extracted data on age, sex, cancer type, comorbidities (excluding suspected diagnoses) on the index date; OAAs prescribed during the non-oral intake period; NGT, gastrostomy or jejunostomy tube placement; and feeding data during hospitalization.

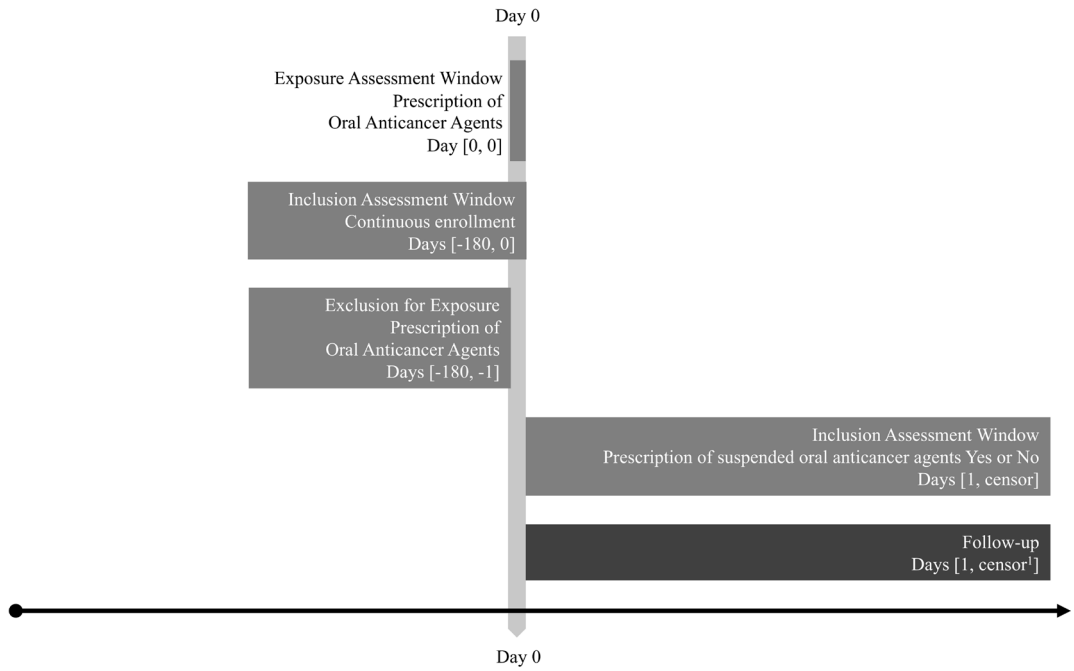
2.3. Impact of the administered OAA suspensions

First, we identified the three most frequent combinations of OAA suspensions and cancer types. For each combination, we classified patients into a suspension group (who received OAA suspensions at least once during the treatment period) and non-suspension group (who never received OAA suspensions). We extracted the following data and compared overall survival (OS) between the two groups: age, sex, and cancer type at the time of initial OAA prescription; confirmed (non-suspected) disease names, prescription records, and medical procedures from 180 days before the initial prescription; and disease name, prescription records, medical procedures, and mortality data following the initial prescription. The index date was defined as the start date of the OAA prescription, and the end of the observation period was defined as the date of death or censoring (Figure 1). OAAs were prescribed during the non-oral intake period; data on NGT, gastrostomy, or jejunostomy tube placement and feeding data during hospitalization were also obtained.

2.4. Definitions of the non-oral intake period and OAA suspensions

In this study, we utilized claims data from the Japanese medical insurance system, using procedure codes as indicators to indirectly identify patients' treatment status and clinical conditions. These codes are standardized classifications used by medical institutions for reimbursement purposes and are calculated based on specific medical procedures or patient conditions. In Japan, a meal fee is charged each time a patient consumes food orally during hospitalization. Similarly, when a patient is unable to eat orally and receives liquid nutrition *via* a tube, a different meal fee applicable to non-oral intake is applied.

The non-oral intake period was defined as the duration during which the procedure code indicating enteral nutrition through a feeding tube (Procedure Code J120 from the Japanese Health Insurance System) was recorded after NGT, gastrostomy, or jejunostomy tube placement (Procedure Codes J0342, K664, and K725).



[1] Censor on death, deregistration from health insurance, or end of study period

Figure 1. Study design applied to the information in the commercial claims database with data observability lines to evaluate the impact of the administration of oral anticancer agent suspensions on overall survival.

Any OAA prescribed during this non-oral intake period was considered to be administered *via* suspension.

2.5. Outcomes

2.5.1. Survey of the real-world use of OAA suspensions in Japan

We assessed the clinical characteristics of patients who were administered OAA suspensions, including sex, age, cancer type, route of administration of the OAA suspension, and comorbidities at the time of suspension administration.

2.5.2. Review of alternative routes for OAAs

A summary of product characteristics (SPC) from Japan, European Medicines Agency (EMA), and U.S. Food and Drug Administration (FDA) was made. We reviewed the latest SPC issued by the Japanese regulatory authority, EMA, and FDA for each OAA administered as a suspension during the study period to determine whether suspension or crushing methods for administration were mentioned.

2.5.3. Impact of OAA suspension administration on survival

Among the combinations of OAA suspensions and cancer types, the three most frequently prescribed combinations were identified. Patients were categorized into the suspension and non-suspension groups, and OS was compared from the date of the initial prescription of the OAA until death or censoring.

2.6. Statistical analysis

We evaluated the prescription trends of OAA suspensions during hospitalization between April 2014 and August 2023. Actual usage patterns based on the clinical characteristics of the patients at the time of the initial suspension administration were summarized using descriptive statistics. Continuous variables are presented as medians with interquartile ranges (IQR). Suspension and non-suspension groups were compared using the Mann–Whitney *U* test. Categorical variables are expressed as frequencies and percentages (n [%]). We conducted a survival comparison between the suspension and non-suspension groups using 1:2 propensity score matching for the three most frequently prescribed OAA suspensions (*9*). Kaplan–Meier survival curves were plotted, and the log-rank test was used for comparisons. All analyses were performed using EZR (version 2.9-1; Saitama Medical Center, Jichi Medical University, Saitama, Japan) (*10*). Statistical significance was set at $p < 0.05$.

2.7. Ethical approval

This study was conducted according to the principles outlined in the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of Meiji Pharmaceutical University (April 14, 2025/ No.202466).

3. Results

3.1. Survey of the real-world use of OAA suspensions in Japan

Between April 2014 and August 2023, 25,252 patients registered in DeSC underwent NGT, gastrostomy, or jejunostomy tube placement. Among them, 126 patients were prescribed OAAs during the non-oral intake period (Figure 2), 62.0% underwent gastrostomy tube placement, and 38.0% underwent NGT placement. No patient who underwent jejunostomy tube placement received OAA suspensions. The median patient age was 76.0 years and 53.2% were men. Brain tumors were the most common primary cancer (23.0%), followed by lung cancer (20.6%), leukemia (15.1%), and thyroid cancer (14.3%) (Table 1).

Thirty-one different OAAs were administered as a suspension. The most common drug suspensions included temozolomide (29 cases), lenvatinib (18 cases), osimertinib (14 cases), imatinib (eight cases), and gefitinib, estramustine, and capecitabine (five each) (Table 2). The route of administration varied depending on the drug used. Temozolomide and imatinib were more typically administered *via* NGT, whereas lenvatinib, osimertinib, gefitinib, estramustine, and capecitabine were mainly administered *via* gastrostomy tubes.

3.2. Review of alternative routes for OAAs based on SPCs from Japan, EMA, and FDA

There were no descriptions of alternative administration methods involving suspension or crushing for non-oral routes in the Japanese SPCs for all 31 OAAs administered by the suspension method. For lenvatinib, osimertinib, imatinib, gefitinib, capecitabine, tepotinib, and nilotinib, the SPCs from the FDA and EMA included instructions on alternative administration methods. Ibrutinib and bosutinib had such instructions only in the FDA SPC, whereas afatinib had instructions only in the EMA documentation. Additionally, while case reports have documented the non-oral administration of tirabrutinib, alectinib, erlotinib, TS-1, and venetoclax, the Japanese, FDA, or EMA SPCs did not include instructions for the preparation for non-oral administration.

3.3. Impact of the administration of OAA suspension on survival

The three most frequent combinations of OAA suspensions and cancer types were temozolomide

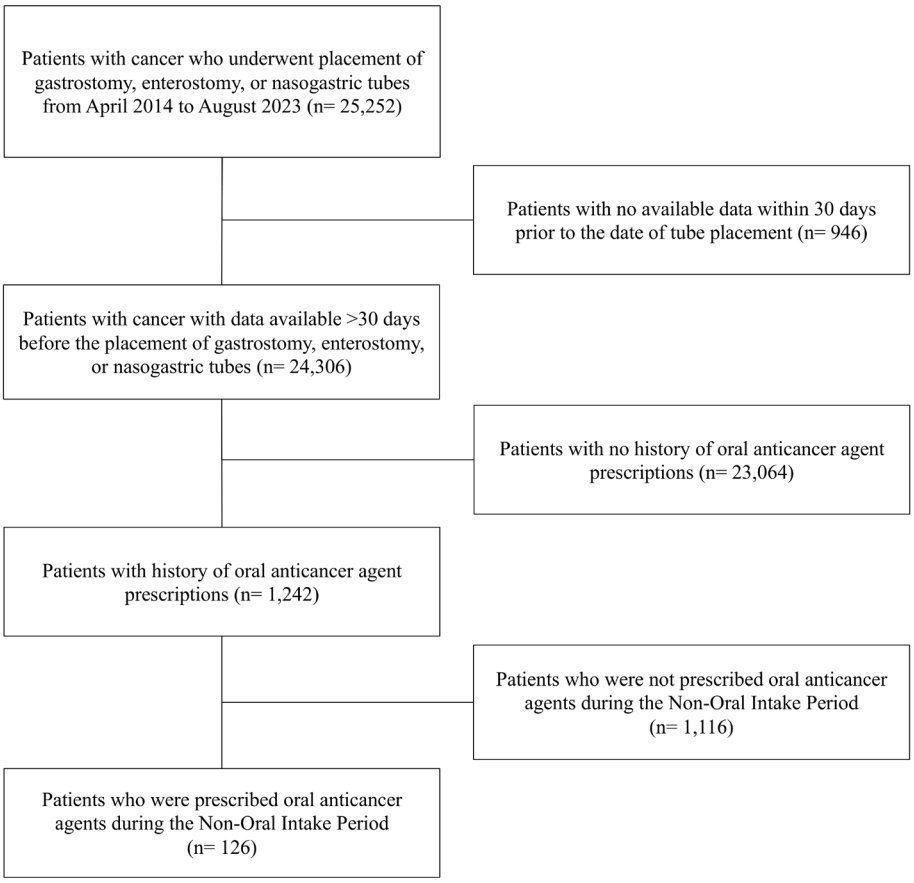


Figure 2. Flowchart of patients included in the study.

Table 1. Patient characteristics

	Total, n (%) 126
Male sex	67 (53.2)
Age: median (IQR)	76.0 (71.0–80.0)
Type of cancer	
Brain and central nervous system	29 (23.0)
Lung	26 (20.6)
Leukemia	19 (15.1)
Thyroid	18 (14.3)
Non-Hodgkin lymphoma	7 (5.6)
Prostate	6 (4.8)
Stomach	5 (4.0)
Gastrointestinal stromal tumor	4 (3.2)
Multiple myeloma	4 (3.2)
Breast	2 (1.6)
Liver	1 (0.8)
Uterine leiomyosarcoma	1 (0.8)
Esophagus	1(0.8)
Renal	1 (0.8)
Larynx	1 (0.8)
Colon	1 (0.8)
Route of administration	
Gastrostomy	78 (61.9)
Nasogastric tube	48 (38.1)
CCI on the index date	
Cerebral vascular accident	41 (32.5)
Metastatic cancer	38 (30.2)
Peptic ulcer	37 (29.4)
Congestive heart failure	31 (24.6)
Pulmonary disease	31 (24.6)
Diabetes	19 (15.1)
Renal disease	11 (8.7)
Liver disease	7 (5.6)
Acute myocardial infarction	4 (3.2)
Paraplegia	4 (3.2)
Diabetes complications	3 (2.4)
Peripheral vascular disease	3 (2.4)
Connective tissue disorder	2 (1.6)
Dementia	2 (1.6)
Severe liver disease	1 (0.8)

IQR, interquartile range; CCI, Charlson comorbidity index.

for brain and central nervous system (CNS) tumors, lenvatinib for thyroid cancer, and osimertinib for lung cancer. Patient backgrounds before and after 1:2 propensity score matching for these three combinations are shown in Table 3. Using sex, age, and treatment duration as covariates, all standardized differences between the two groups were < 1 after matching. Figure 3 presents the results of the survival analysis following propensity score matching. For temozolomide and lenvatinib, survival did not differ between the suspension and non-suspension groups. In contrast, the osimertinib suspension group had a shorter survival duration than the non-suspension group ($p = 0.047$).

4. Discussion

To our knowledge, this is the first study to clarify the real-world use of OAA suspensions using a large Japanese administrative claims database. Temozolomide was the most commonly used agent, followed by lenvatinib and osimertinib, with most administered through gastrostomy tubes. No Japanese SPC included instructions for suspension, although FDA and EMA SPCs offered some guidance. OS did not differ significantly between the suspension and non-suspension groups for temozolomide and lenvatinib. However, for osimertinib, the suspension group showed significantly shorter OS compared to the non-suspension group. This finding should be interpreted with caution, as the selection of patients for suspension administration likely reflects a more advanced disease status, poor performance status, or terminal-stage care. These potential confounding factors were not fully adjusted for in the propensity score matching. Therefore, this result should be viewed as an observational finding, rather than as evidence of harmful impact or ineffectiveness of suspension administration.

Patients who received suspensions were predominantly older adults (median age 76.0 years), aligning with the findings of Sako *et al*., who reported a median age of 80.0 years among patients undergoing gastrotomy or jejunostomy tube placements (*11*). They also noted cerebrovascular disease, aspiration pneumonia, dementia, neuromuscular disease, and malignancy as the key underlying conditions. Similarly, in this study, many patients who underwent NGT or gastrostomy tube placement were found to have comorbidities other than malignancies, including cerebrovascular accidents, metastatic cancer, peptic ulcers, congestive heart failure, and pulmonary disease. In contrast, only two patients (1.6%) had dementia during the initiation of OAA suspension, possibly indicating a reluctance to administer chemotherapy to patients with dementia. Boakye *et al*. reported that dementia was the comorbidity most strongly associated with non-receipt of chemotherapy compared to other conditions, such as heart failure or stroke (*12*).

Temozolomide suspension, the most frequently used agent, remains physically and chemically stable for up to 14 days under refrigeration (*13*). The temozolomide suspension developed by Annereau *et al.* by decapsulating the capsule contents is suitable for administration *via* NGT (*14*). However, SPCs for temozolomide from Japan, the FDA, and EMA do not include information regarding alternative administration methods for patients who cannot orally consume the drug. This omission may be attributed to the availability of an injectable formulation of temozolomide developed specifically for such patients (*15*). Nevertheless, only one of the 29 patients receiving oral temozolomide in our study was switched to the injectable form. Given its proven stability (*13,14*), temozolomide suspension may retain sufficient efficacy. Survival analysis comparing the suspension and non-suspension groups of patients with brain and CNS tumors revealed no significant differences in OS. Prophylactic gastrostomy tube placement in patients with head and neck cancer helps in maintaining adequate nutritional status (*16*). Therefore, in this study,

Table 2. Types of oral anticancer agent suspensions

Oral anticancer agent suspensions	Type of cancer	n	Route of administration	n	Japan	FDA	EMA	Case Report
Temozolomide	Brain and central nervous system	29	Gastrostomy	12	None	None	None	None
			Nasogastric tube	17				
Lenvatinib	Thyroid	17	Gastrostomy	16	None	○	○	○
	Liver	1	Nasogastric tube	2				
Osimertinib	Lung	14	Gastrostomy	12	None	○	○	○
			Nasogastric tube	2				
Imatinib	Leukemia	4	Gastrostomy	3	None	○	○	○
	Gastrointestinal stromal tumor	4	Nasogastric tube	5				
Gefitinib	Lung	5	Gastrostomy	4	None	○	○	○
			Nasogastric tube	1				
Estramustine	Prostate	5	Gastrostomy	5	None	None	Not approved	None
			Nasogastric tube	0				
Capecitabine	Stomach	3	Gastrostomy	3	None	○	○	None
	Colon	1	Nasogastric tube	2				
	Esophagus	1						
Tirabrutinib	Non-Hodgkin lymphoma	4	Gastrostomy	2	None	Not approved	Not approved	○
			Nasogastric tube	2				
Tegafur/Uracil	Breast	2	Gastrostomy	4	None	Not approved	Not approved	None
	Prostate	1	Nasogastric tube	0				
	Larynx	1						
Cyclophosphamide	Leukemia	1	Gastrostomy	0	None	None	Not approved	None
	Multiple myeloma	1	Nasogastric tube	3				
	Non-Hodgkin lymphoma	1						
Dasatinib	Leukemia	3	Gastrostomy	1	None	None	None	None
			Nasogastric tube	2				
Melphalan	Multiple myeloma	3	Gastrostomy	2	None	None	Not approved	None
			Nasogastric tube	1				
Alectinib	Lung	2	Gastrostomy	1	None	None	None	○
			Nasogastric tube	1				
Ibrutinib	Leukemia	1	Gastrostomy	1	None	○	None	○
	Non-Hodgkin lymphoma	1	Nasogastric tube	1				
Erlotinib	Lung	2	Gastrostomy	2	None	None	None	○
			Nasogastric tube	0				
Dacomitinib	Lung	2	Gastrostomy	2	None	None	None	None
			Nasogastric tube	0				
TS-1	Stomach	2	Gastrostomy	2	None	Not approved	None	○
			Nasogastric tube	0				
Tretinoin	Leukemia	2	Gastrostomy	0	None	None	Not approved	None
			Nasogastric tube	2				
Bosutinib	Leukemia	2	Gastrostomy	1	None	○	None	None
			Nasogastric tube	1				

FDA, U.S. Food and Drug Administration; EMA, European Medicines Agency.

Table 2. Types of oral anticancer agent suspensions (continued)

Oral anticancer agent suspensions	Type of cancer	n	Route of administration	n	Japan	FDA	EMA	Case Report
Ponatinib	Leukemia	2	Gastrostomy	2	None	None	None	None
			Nasogastric tube	0				
Afatinib	Lung	1	Gastrostomy	1	None	None	○	None
Axitinib	Renal	1	Nasogastric tube	1	None	None	None	None
Sorafenib	Thyroid	1	Gastrostomy	1	None	None	None	None
Trifluridine and Tipiracil	Colon	1	Gastrostomy	1	None	None	None	None
Tepotinib	Lung	1	Nasogastric tube	1	None	○	○	None
Nilotinib	Leukemia	1	Nasogastric tube	1	None	○	○	None
Nintedanib	Leukemia	1	Gastrostomy	1	None	None	None	None
Pazopanib	Uterine leiomyosarcoma	1	Nasogastric tube	1	None	None	None	None
Procarbazine	Non-Hodgkin lymphoma	1	Nasogastric tube	1	None	None	Not approved	None
Venetoclax	Leukemia	1	Nasogastric tube	1	None	None	None	○
Methotrexate	Leukemia	1	Gastrostomy	1	None	None	Not approved	None

FDA, U.S. Food and Drug Administration; EMA, European Medicines Agency.

prophylactic gastrostomy tube placement may have enabled continued treatment with suspensions, thereby contributing to survival.

Lenvatinib suspension has been administered *via* NGT with favorable outcomes in patients with thyroid cancer (*17,18*). This may explain the frequent use of lenvatinib in our thyroid cancer cohort. The FDA and EMA SPCs describe this method, although no randomized trials or bioequivalence data are available. In our study, OS did not differ significantly between the lenvatinib suspension and non-suspension groups among patients with thyroid cancer. Multiple case reports support the effectiveness of enteral lenvatinib in thyroid cancer (*17,18*). In particular, for anaplastic thyroid cancer, rapid tumor growth in the neck may prevent oral intake of medications, and enteral administration of lenvatinib suspension reduces the tumor size and improves prognosis (*18*). Similar to previous case reports, we found that among patients receiving lenvatinib, the median duration from treatment initiation to the start of suspension administration was 2.5 days (IQR: 0.0–59.8), suggesting that oral intake challenges often emerged at an early stage during therapy. Despite early difficulties in oral intake, treatment may be continued through alternative administration of suspensions. This potential continuation of therapy may have contributed to no significant differences in OS between the suspension and non-suspension groups, suggesting that suspension did not adversely affect survival.

Cases of osimertinib administration *via* suspension have been reported (*19,20*). This method is described in SPCs by the FDA and EMA, similar to lenvatinib. However, the efficacy and bioequivalence of osimertinib suspension have not been validated. Notably, patients with lung cancer receiving osimertinib suspension had significantly shorter survival compared to those receiving it intact. The median time from treatment initiation to suspension administration was longer in the osimertinib group (median: 668.5 days; IQR: 106.2–1129.8) than in the temozolomide (median: 17.0 days, IQR: 8.0–72.0; p value = 0.005) and lenvatinib (median: 19.0 days, IQR: 0.5–158.8, p value = 0.049) groups. Furthermore, brain metastases were observed in four of the 10 patients in the osimertinib suspension group. Considering the high CNS penetrability and efficacy of osimertinib against leptomeningeal metastases (*21*), many patients in this group were likely unable to receive the medication orally because of terminal disease progression and poor general health. Patients with lung cancer and leptomeningeal metastases frequently present with poor performance status (PS) and dysphagia (*20*), which may contribute to their shorter survival. These background factors underscore the importance of not attributing the shorter survival observed in the osimertinib suspension group to the administration method itself. Rather, they highlight the need for clinical awareness of the severe condition of such patients. This study was a descriptive

Table 3. Characteristics of patients treated with the top three oral anticancer drugs before and after propensity score matching

	Before propensity score matching			After propensity score matching		
	Suspension group	Non-suspension group	SMD	Suspension group	Non-suspension group	SMD
Temozolomide						
Total, n	1145			63		
n	23	1122		21	42	
Male sex	12 (52.2)	591 (52.7)	0.010	11 (52.4)	22 (52.4)	< 0.001
Age: median (IQR)	79.0 (76.0–80.0)	76.0 (68.0–80.0)	0.709	78.0 (76.0–80.0)	78.0 (76.0–80.0)	0.007
Treatment duration: median (IQR)	160.0 (51.0–310.0)	155.5 (42.0–337.0)	0.121	160.0 (47.0–308.0)	155.5 (47.3–309.3)	0.002
Lenvatinib						
Total, n	537			30		
n	12	525		10	20	
Male sex	4 (33.3)	194 (37.0)	0.076	3 (30.0)	6 (30.0)	< 0.001
Age: median (IQR)	76.0 (70.0–80.0)	76.0 (69.0–81.0)	0.208	76.0 (69.0–80.3)	76.0 (70.3–80.0)	0.030
Treatment duration: median (IQR)	177.0 (16.8–550.3)	246.0 (50.0–627.0)	0.337	177.0 (34.3–609.8)	156.5 (19.5–565.3)	0.015
Osimertinib						
Total, n	5116			30		
n	10	5106		10	20	
Male sex	3 (30.0)	1763 (34.6)	0.097	3 (30.0)	6 (30.0)	< 0.001
Age: median (IQR)	74.0 (70.3–79.3)	78.0 (72.0–82.0)	0.346	74.0 (70.3–79.3)	74.0 (71.0–79.0)	< 0.001
Treatment duration: median (IQR)	222.0 (31.8–465.5)	269.5 (74.0–609.0)	0.341	222.0 (31.8–465.5)	213.5 (36.8–423.8)	0.011

SMD; standardized mean difference; IQR, interquartile range.

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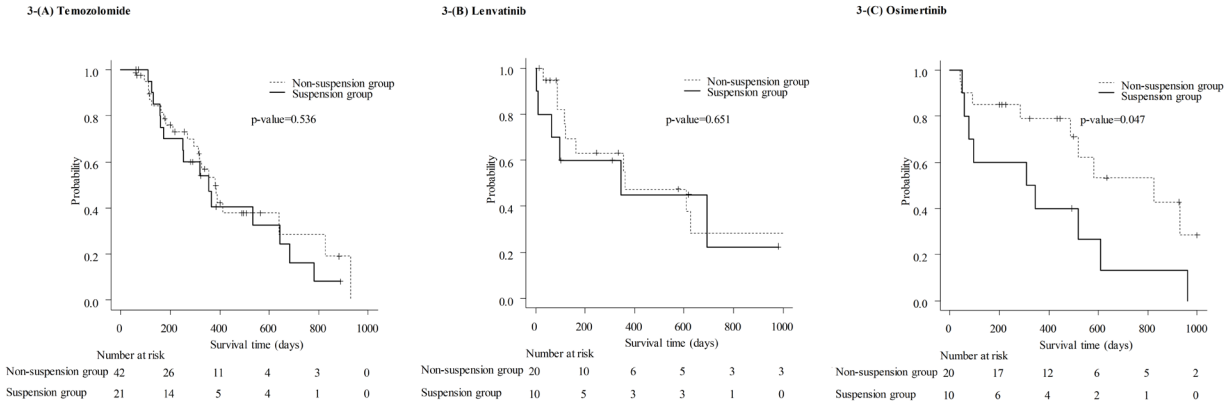

Figure 3. Kaplan–Meier curves for overall survival. (A) Patients with brain and central nervous system tumors treated with temozolomide; (B) Patients with thyroid cancer treated with lenvatinib; (C) Patients with lung cancer treated with osimertinib.

investigation of the nationwide use of the suspension method for OAAs and was not designed to directly assess the efficacy or safety. Nonetheless, by leveraging large-scale claims data, it evaluated treatment practices in under-represented populations in real-world settings, such as those with dysphagia and poor general health. Suspension administration may enable continued therapy when oral intake is difficult, provided the patient's overall condition is carefully considered. Multidimensional patient assessments and pharmacotherapeutic strategies tailored to individual preferences and treatment goals are essential. Insights from this study may support informed decision-making in complex clinical scenarios.

Regarding imatinib, adequate plasma concentrations were achieved *via* suspension through a gastrostomy tube (*22*). Case reports have documented that gefitinib administration *via* either a gastrostomy tube or NGT causes tumor shrinkage (*23-25*). No serious adverse events were reported. Pharmacokinetic studies demonstrated no significant differences in the area under the curve and maximum plasma concentration between the suspensions and intact formulations (*26*). The pharmacokinetics, efficacy, and safety of imatinib and gefitinib were evaluated when administered *via* suspension through enteral feeding tubes, and the results support suspension as an alternative route. Conversely, although estramustine and capecitabine are frequently administered as a suspension, case reports or pharmacokinetic studies on the efficacy or safety of their suspension are lacking. For drugs such as TS-1, alectinib, ibrutinib, erlotinib, tirabrutinib, and venetoclax, case reports where suspensions were administered *via* enteral routes have shown treatment efficacy in tumor reduction or improvement in PS (*27-36*). However, these reports were limited to individual cases, and comprehensive data on the stability, absorption, and long-term safety of suspensions are lacking. Therefore, from a pharmacist's perspective, proactively recommending a suspension of OAAs is challenging.

Suspension of OAAs is an important alternative route for patients who cannot swallow because of dysphagia or other medical conditions. Several case reports have supported its efficacy (*17-20,23-25,27-36*), and some SPCs explicitly describe alternative administration procedures. However, the risks of exposure to healthcare providers and caregivers during preparation remain understudied. When capsules or tablets are opened and crushed, drug particles may become airborne, risking contact with skin, mucosa, or inhalation (*37*), which is particularly concerning for highly toxic agents. The National Institute for Occupational Safety and Health and the American Society of Health-System Pharmacists strongly recommend the use of biological safety cabinets and personal protective equipment when preparing these agents (*38,39*). In Japan, the SSM minimizes exposure risk by avoiding tablets. However, studies evaluating the extent of exposure associated with the preparation and administration of OAA suspensions using this method are lacking. Therefore, careful handling is warranted during preparation and administration. Future research should address the stability of each suspension and the associated exposure risks to establish safe preparation methods and administration protocols.

This study has some limitations. First, the claims database lacks detailed information on cancer stage, PS, and rationale for suspension administration, limiting casual interpretation. Second, we could not identify patients who received anticancer suspensions orally without tube placement, or those receiving enteral therapy alongside total parenteral nutrition. Third, data on suspension methods (*e.g.*, use of SSM, medium used, preparation steps, or tube type) were unavailable. In addition, the definition of "suspension administration" in this study was inferred based on the overlap between the health insurance procedure codes for enteral nutrition and records of oral anticancer agent prescriptions. However, direct confirmation was not possible as specific prescription orders or procedure records were

not available. This indirect classification method may have introduced misclassification bias and limited the precision of identifying true suspension administration. Therefore, these results should be interpreted taking into account the potential for exposure misclassification inherent in claims-based analyses. These limitations are inherent in claims-based studies. Future studies using clinical records are warranted to validate these findings.

In summary, for patients with cancer experiencing dysphagia, suspension administration offers a valuable treatment option. However, drug stability, safety, and exposure risk must be considered. Scientific evidence remains limited for many agents, highlighting the need for careful, individualized clinical judgement. Healthcare professionals must manage suspension therapy comprehensively, including indication, preparation, safety measures, and caregiver education. Accumulating pharmacological evidence and developing evidence-based guidelines tailored to clinical practice will be essential for safe and effective implementation.

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References

1. Kav S, Fleury M, Fernandez-Ortega P, Manzullo EF, Kerr KA, DeGennaro R, Ginex PK. 15 years supporting adherence to oral anti-cancer treatment: use of the MASCC Oral Agent Teaching Tool (MOATT) worldwide, a review for the future. Support Care Cancer. 2025; 33:229.
2. Tomonaga I, Koseki H, Imai C, Shida T, Nishiyama Y, Yoshida D, Yokoo S, Osaki M. Incidence and characteristics of aspiration pneumonia in the Nagasaki Prefecture from 2005 to 2019. BMC Pulm Med. 2024; 24:191.
3. Abe T, Kusakabe S, Naoi M, Suzuki T, Sagara A, Hiraide M, Sano M, Nakayama T. Evaluation of the simple suspension method for oral anticancer drugs. Yakugaku Zasshi. 2024; 144:441-445.
4. Dziewas R, Beck AM, Clave P, Hamdy S, Heppner HJ, Langmore SE, Leischker A, Martino R, Pluschinski P, Roesler A, Shaker R, Warnecke T, Sieber CC, Volkert D, Wirth R. Recognizing the importance of dysphagia: stumbling blocks and stepping stones in the twenty-first century. Dysphagia. 2017; 32:78-82.
5. Martino R, Foley N, Bhogal S, Diamant N, Speechley M, Teasell R. Dysphagia after stroke: incidence, diagnosis, and pulmonary complications. Stroke. 2005; 36:2756-2763.
6. Pei R, Wang D. Prognostic nutritional index negative associated with mortality in older Japanese patients with dysphagia. Front Nutr. 2025; 12:1586248.
7. ASGE Standards of Practice Committee; Jain R, Maple JT, *et al*. The role of endoscopy in enteral feeding. Gastrointest Endosc. 2011; 74:7-12.
8. Volkert D, Berner YN, Berry E, *et al*. ESPEN Guidelines on Enteral Nutrition: Geriatrics. Clin Nutr. 2006; 25:330-360.
9. Austin PC. Statistical criteria for selecting the optimal number of untreated subjects matched to each treated subject when using many-to-one matching on the propensity score. Am J Epidemiol. 2010; 172:1092-1097.
10. Kanda Y. Investigation of the freely available easy-to-use software 'EZR' for medical statistics. Bone Marrow Transplant. 2013; 48:452-458.
11. Sako A, Yasunaga H, Horiguchi H, Fushimi K, Yanai H, Uemura N. Prevalence and in-hospital mortality of gastrostomy and jejunostomy in Japan: a retrospective study with a national administrative database. Gastrointest Endosc. 2014; 80:88-96.
12. Boakye D, Nagrini R, Ahrens W, Haug U, Gunther K. The association of comorbidities with administration of adjuvant chemotherapy in stage III colon cancer patients: a systematic review and meta-analysis. Ther Adv Med Oncol. 2021; 13:1758835920986520.
13. Trissel LABRF, Zhang YB, Koontz SEPB. Temozolomide stability in extemporaneously compounded oral suspensions. Int J Pharm Compd. 2006; 10:396-399.
14. Annereau M, Hinterlang M, Bienayme H, Vassal G, Pinon A, Schmitt M, Denis L, Lemarchand C, Martin L, Lemare F, Abbou S, Bastid J, Tortolano L. Development of a hospital compounded, taste-masked, temozolomide oral suspension and 5-year real-life experience in treating paediatric patients. Pharmaceuticals (Basel). 2022; 15:555.
15. Diez BD, Statkevich P, Zhu Y, Abutarif MA, Xuan F, Kantesaria B, Cutler D, Cantillon M, Schwarz M, Pallotta MG, Ottaviano FH. Evaluation of the exposure equivalence of oral versus intravenous temozolomide. Cancer Chemother Pharmacol. 2010; 65:727-734.
16. Almeida ND, Yu H, Iovoli AJ, Fang M, Schrand TV, Pepin A, Gupta V, Wooten KE, Markiewicz MR, McSpadden RP, Hicks WL, Jr., Farrugia MK, Singh AK. Prophylactic gastrostomy tube during chemoradiation for head and neck cancer decreases weight loss but increases rate of tube use beyond six months. Oral Oncol. 2025; 160:107136.
17. Molinaro E, Viola D, Viola N, Falcetta P, Orsolini F, Torregrossa L, Vagli P, Ribechini A, Materazzi G, Vitti P, Elisei R. Lenvatinib administered *via* nasogastric tube in poorly differentiated thyroid cancer. Case Rep Endocrinol. 2019; 2019:6831237.
18. Kawano F, Yonekawa T, Yamaguchi H, Shibata N, Tashiro K, Ikenoue M, Munakata S, Higuchi K, Tanaka H, Sato Y, Hosokawa A, Takeno S, Nakamura K, Nanashima A. Nasogastric administration of lenvatinib solution in a mechanically ventilated patient with rapidly growing anaplastic thyroid cancer. Endocrinol Diabetes Metab Case Rep. 2020; 2020.
19. Tani N, Takatsuka S, Kataoka N, Kunimatsu Y, Tsutsumi R, Sato I, Tanimura M, Nakano T, Tanimura K, Kato D, Takeda T. Nasogastric administration of osimertinib suspension for an epidermal growth factor receptor-mutated lung cancer causing an esophageal stricture: case report. Ann Palliat Med. 2022; 11:1542-1545.
20. Takeda T, Itano H, Takeuchi M, Nishimi Y, Saitoh M, Takeda S. Osimertinib administration *via* nasogastric tube in an EGFR-T790M-positive patient with leptomeningeal metastases. Respirol Case Rep. 2017; 5:e00241.
21. Ballard P, Yates JW, Yang Z, *et al*. Preclinical comparison of osimertinib with other EGFR-TKIs in EGFR-mutant NSCLC brain metastases models, and early evidence of clinical brain metastases activity. Clin Cancer Res. 2016; 22:5130-5140.

22. Fiebrich-Westra HB, Visser O, Francken AB, Smolders EJ. Alternative routes of drug administration: exposure of imatinib using different formulations. Cancer Chemother Pharmacol. 2025; 95:45.
23. Okuda T, Hayashi H, Fujita M, Yoshioka H, Tasaki T, Nakagawa K, Kato A. Administration of gefitinib *via* nasogastric tube effectively improved the performance status of a patient with lung adenocarcinoma-derived meningeal carcinomatosis. Int Cancer Conf J. 2014; 3:211-214.
24. Suzumura T, Yonesaka K, Tsukuda H, Fukuoka M. Successful gefitinib treatment administration *via* gastrostomy tube in a patient with non-small cell lung cancer with dysphagia. BMJ Case Rep. 2014; 2014:bcr2013202705.
25. Uruga H, Moriguchi S, Takahashi Y, Ogawa K, Murase K, Mochizuki S, Hanada S, Takaya H, Miyamoto A, Morokawa N, Kishi K. Gefitinib successfully administered in a lung cancer patient with leptomeningeal carcinomatosis after erlotinib-induced pneumatosis intestinalis. BMC Cancer. 2018; 18:825.
26. Cantarini MV, McFarquhar T, Smith RP, Bailey C, Marshall AL. Relative bioavailability and safety profile of gefitinib administered as a tablet or as a dispersion preparation *via* drink or nasogastric tube: results of a randomized, open-label, three-period crossover study in healthy volunteers. Clin Ther. 2004; 26:1630-1636.
27. Okita A, Miyade Y, Okano K. Effective management of an advanced gastric cancer patient by TS-1 combined chemotherapy using nasojejunal tube and successful transfer to home care after percutaneous transesophageal gastro-tubing (PTEG): a case report. Acta Med Okayama. 2010; 64:67-70.
28. Hirano K, Nakamura K, Hasegawa M. Pharmacokinetics and adverse event of TS-1 administered through gastrostomy. Gan To Kagaku Ryoho. 2005; 32:859-862.
29. Hagiike M, Tsuboi Y, Akamoto S, Yachida S, Izuishi K, Karasawa Y, Goda F, Okada S, Usuki H, Maeta H. TS-1 therapy *via* intestinal catheter used for tube feeding in a patient with gastric cancer after total gastrectomy. Gan To Kagaku Ryoho. 2005; 32:1033-1036.
30. Thomas QD, Pautas M, Guilhaume MN, Fiteni F, Ge T, Girard N. Enteral administration of alectinib for ALK-positive non-small cell lung cancer in an elderly patient: A case report. Medicine (Baltimore). 2021; 100:e27611.
31. Kanai O, Kim YH, Nakatani K, Fujita K, Mio T. Nasogastric tube-administered alectinib achieved long-term survival in a crizotinib-refractory nonsmall cell lung cancer patient with a poor performance status. Clin Case Rep. 2017; 5:927-930.
32. Alsuliman T, Belghoul M, Choufi B. Ibrutinib treatment through nasogastric tube in a comatose patient with central nervous system localization of mantle cell lymphoma. Case Rep Hematol. 2018; 2018:5761627.
33. Bosch-Barrera J, Sais E, Lorencio C, Porta R, Izquierdo A, Menendez JA, Brunet J, Sirvent JM, Rosell R. Successful empirical erlotinib treatment of a mechanically ventilated patient newly diagnosed with metastatic lung adenocarcinoma. Lung Cancer. 2014; 86:102-104.
34. Yoshioka H, Okuda T, Nakao T, Fujita M, Takahashi JC. Experience with tirabrutinib in the treatment of primary central nervous system lymphoma that is difficult to treat with standard treatment. Anticancer Res. 2022; 42:4173-4178.
35. Yoshioka H, Okuda T, Nakao T, Fujita M, Takahashi JC. Experience with nasogastric tube administration of tirabrutinib in the treatment of an elderly patient with primary central nervous system lymphoma. Int Cancer Conf J. 2021; 10:290-293.
36. Sato H, Kobayashi T, Fujita N, Yamashita T, Kitadate A, Yoshioka T, Nara M, Kameoka Y, Miura M, Takahashi N. Safe administration and pharmacokinetic monitoring of crushed venetoclax tablets with posaconazole and clarithromycin *via* percutaneous endoscopic gastrostomy tube in a patient with acute myeloid leukemia. Cancer Chemother Pharmacol. 2022; 90:279-284.
37. Sugiura S, Asano M, Kinoshita K, Tanimura M, Nabeshima T. Risks to health professionals from hazardous drugs in Japan: a pilot study of environmental and biological monitoring of occupational exposure to cyclophosphamide. J Oncol Pharm Pract. 2011; 17:14-19.
38. Managing Hazardous Drug Exposures: Information for Healthcare Settings. *https://www.cdc.gov/niosh/docs/2023-130/default.html* (accessed December 4, 2025).
39. Power LA, Coyne JW. ASHP guidelines on handling hazardous drugs. Am J Health Syst Pharm. 2018; 75:1996-2031.

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