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REVIEW
Bilingual edition English/Spanish

A guide for the administration of oral antineoplastic in patients with swallowing disorders

Guía de administración de antineoplásicos orales en pacientes con trastornos de la deglución

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Abstract

Objective: To review the available literature on the administration of oral antineoplastic drugs in patients with swallowing disorders and systematize the information obtained.

Method: Between September 2019 and April 2020, two hospital pharmacists drew up a list of the oral antineoplastic drugs available in Spain, which was then distributed to three hospital pharmacists, each of whom carried out a literature search and a review. An analysis was made of the prescribing information and searches were performed in Pubmed, Micromedex, Uptodate, the Cancer Care Ontario website, different pharmaceutical bulletins, feeding tube administration guidelines, and tertiary information sources. Lastly, the pharmaceutical industry was contacted. The group systematized the information obtained, after which a fourth hospital pharmacist and an independent physician reviewed the work carried out.

Results: A total of 64 oral antineoplastic drugs were reviewed. Relevant information was obtained for 48 drugs, of which 44 were amenable to administration to these patients (69% of the investigated drugs). A systematization of the information found was carried out.

Conclusions: Despite having found different methods for preparing and administering most of the oral antineoplastic drugs reviewed, the information compiled was rather scarce and with a low level of evidence. Further

Resumen

Objetivo: Revisar la literatura disponible sobre la administración de antineoplásicos orales en pacientes con trastornos de la deglución y realizar una síntesis de la información hallada.

Método: En el periodo septiembre 2019-junio 2020, tres farmacéuticos hospitalarios elaboraron una lista con los antineoplásicos orales disponibles en España, la cual fue repartida, y cada cual llevó a cabo la búsqueda y revisión bibliográfica de los medicamentos asignados. Se revisaron las fichas técnicas y así como Pubmed, Micromedex, Uptodate, la página web del Cancer Care Ontario, diferentes boletines farmacéuticos, guías de administración por sonda y otras fuentes terciarias de información. En último lugar, se contactó con la industria farmacéutica. Posteriormente cada uno sintetizó la información que había hallado y para concluir, un médico y un cuarto farmacéutico hospitalario revisaron todo el trabajo llevado a cabo.

Resultados: Se revisaron un total de 64 fármacos antineoplásicos orales. Se obtuvo información pertinente en el caso de 48, de los cuales 44 presentaban posibilidad de administración en estos pacientes (un 69% de los fármacos investigados). Se realizó una síntesis de la información hallada.

Conclusiones: Pese a haber encontrado posibles métodos de preparación y administración para la mayoría de los antineoplásicos orales revisados, se constata que la información es más bien escasa y con bajo nivel

KEYWORDS
Antineoplastic agents; Oral chemotherapy; Deglutition disorders; Drug compounding; Extemporaneous; Drug administration routes; Gastrointestinal intubation.

PALABRAS CLAVE
Antineoplásicos; Quimioterapia oral; Trastornos de deglución; Preparación de medicamentos; Extemporánea; Vías de administración de medicamentos; Intubación gastrointestinal.

studies, based on pharmacokinetic and stability studies, are necessary in this field as there is a sore need for oral liquid pharmaceutical forms or extemporaneous preparations allowing administration of oral antineoplastic drugs to these patients.

de evidencia. Es necesario seguir investigando en este campo, ya que se precisan formas farmacéuticas líquidas, o preparaciones extemporáneas, que en base a estudios farmacocinéticos y de estabilidad permitan la administración de antineoplásicos orales en este grupo de pacientes.

Introduction

Although elderly patients tend to be underrepresented in clinical trials, they account for a significant proportion of cancer patients[1]. It is undeniable that aging exponentially increases the risk of cancer. Approximately 60% of new cancer cases are diagnosed in persons over 65 years of age[2].

It is a well-known fact that dysphagia is an increasingly serious health problem among our aging population. Age-related changes in the physiology of swallowing and age-related diseases are factors that predispose the elderly to dysphagia. Although there is a dearth of precise data on the prevalence of dysphagia, the most conservative estimations suggest that the condition affects up to 15% of elderly persons[3].

However, cancer patients are not prone to dysphagia only on account of their age. There are also a series of tumors that have been specifically associated with the disorder. In fact, dysphagia is one of the main symptoms of and one of the main obstacles to treatment for several oncological conditions such as head and neck tumors[4], esophagus cancer[5], thyroid cancer, and lymphoma, among others.

Oral therapy is becoming increasingly common in treating oncological and hematological disorders not least because patients have been shown to prefer that route of administration[6]. In 2019, 8 of the 12 new antineoplastics approved by the US Food and Drug Administration were oral compounds[7]. Nonetheless, patients with swallowing difficulties who receive oral chemotherapy may exhibit lack of adherence and require changes or discontinuations in their treatment, which could negatively impact their clinical results[8].

Administration of oral drugs to patients with swallowing problems, who may or may not be on enteral nutritional support, represents a challenge for pharmaceutical care. Generally, solid medications must be crushed or opened, and a suspension/solution is prepared to prevent feeding tube blockage. However, such operations are often ill suited to enteric tablets, and sustained and/or controlled-release formulations[9]. On top of these problems, the label of oral antineoplastics does not usually contain information on the advisability of carrying out such operations. All of this complicates treatment with oral antineoplastics not only in patients with dysphagia, but also in the pediatric population[10], who usually require formulations allowing individualized dosing schemes to ensure drug safety and efficacy.

This is an issue of unquestionable clinical significance as it relates to the effectiveness and/or safety of antineoplastic treatment. Taking into consideration the large number of consultations made to hospital pharmacies about this subject, this review article seeks to compile the literature available with a view to the development of a series of guidelines that may facilitate administration of oral antineoplastics in patients with swallowing disorders.

Methods

In September 2019 a review was carried out of all the oral antineoplastic drugs approved by the European Medicines Agency (EMA), as published on the Agency's website. Subsequently, a list was drawn up of the oral antineoplastics available in Spain. The list was distributed among a group of hospital pharmacists (two specialists and a resident), each being assigned a set of drugs. Between September 2019 and June 2020, the group members compiled all the information available on the drugs assigned to them. Firstly, they reviewed the labels of the different medications to find out whether such labels contained any information regarding the possibility of crushing, opening and/or dispersing them in fluids or food.

In those cases where this information was not available, or where the products' label recommended not to split, open, crush or chew the medication, recourse was made to Pubmed, where the following keywords were searched: "name of the active ingredient", "oral antineoplastics ", "oral chemotherapy", "deglutition disorders", "drug compounding", *"extemporaneous"*, "crush*", "gastrointestinal intubation" and "nasogastric tube". The titles and abstracts of the different publications were reviewed to select those that contained relevant information (case reports on the administration of medication to patients with dysphagia, whether or not on nutritional support; pharmacokinetic studies; studies on the stability of liquid formulations; and any study on extemporaneous liquid dosage forms). The review was completed with searches in other sources such as Micromedex (dosing/administration section); Uptodate (patient information and dosing/administration sections); the Cancer Care Ontario website (drug formulary section); pharmaceutical newsletters and medication fact sheets, such as the ones produced by the Spanish Society of Hospital Pharmacist (SEFH)'s oncological pharmacy (GEDEFO) and pediatric pharmacy (GEFP) groups; guidelines on the administration of drugs through feeding tubes; and other (tertiary) sources of information.

Lastly, and only in the case of drugs where no information was available, contact was established with the pharmaceutical companies that manufacture them, via email or telephone, to gather the required data.

Each group member reviewed and analyzed the literature they had selected on each of the drugs assigned to them. Finally, an independent physician and a fourth pharmacist reviewed the whole work carried out.

Results

A total of 64 oral antineoplastic drugs were reviewed, which are commonly dispensed by Spanish hospital pharmacy departments. Significant information was obtained on 48 of them, of which 44 (69% of the drugs studied) were eligible for administration to patients with a deglutition disorder.

Only one of the drugs (trametinib), available only as a foreign medication, was marketed as an oral liquid formulation. The most commonly used compounding method was dispersion of the solid therapeutic agent in an aqueous solution, with water, simple syrup, Ora-Plus®, and Ora-Sweet® being typically used as solvents. In three cases, a recommendation to dissolve the drug in oil was found; on other occasions drugs were dispersed in apple compote or orange juice. Crushing of the solid form was only recommended for ten medications, and the use of an intravenous formulation as a basis to prepare the oral liquid form was recommended for three drugs.

Certain drugs were associated with more than one compounding method. In these cases, the selected method was always the one supported by the largest body of evidence. When the level of evidence was the same, the method of choice was selected based on criteria related to the complexity or the stability of the formulation.

All the information obtained is summarized in table 1, where the first column contains all the drugs investigated. Each product is described by the name of its active ingredient, its brand name (in brackets) and, when applicable, its generic formulation. The second column describes how antineoplastics may be modified for feeding tube administration, and the third column contains remarks related to the types of containers to be used to store the medication, the most suitable preservation conditions, stability, etc. When no information is provided regarding the period of stability or the expiry of a certain preparation, administration should be initiated immediately following formulation (within one hour).

Discussion

The presence of dysphagia, compounded by the unavailability of oral liquid antineoplastic formulations, brings to the forefront the need to seek extemporaneous methods to prepare and administer oral antineoplastics in patients with deglutition disorders. The problem is that, in the majority of cases, the manufacturers of these products do not provide information on how to modify them for feeding tube administration, which makes it necessary to search the literature for answers.

Some clinical studies have been published on the subject, as well as stability analyzes and pharmacokinetic reports, but few of them provide information on the way in which the drug is to be modified. Oral liquid preparations of antineoplastic drugs based on stability data are unusual, most of them being extemporaneous formulations for immediate administration[13,15].

Table 1. Overview of the administration of oral antineoplastics in patients with deglutition disorders

Drug	Dosage form modifications*	Remarks
ABIRATERONE film-coated tablets (Zytiga®)	Not recommended.	The manufacturer recommends crushing or dissolving the product due to a potential decrease in efficacy.
AFATINIB film-coated tablets (Giotrif®)	Dissolve the required tablets in hot water at 55 °C[11].	Tested for feeding tube administration.
ALECTINIB hard capsules (Alecensa®)	Method 1 (preferred): Prepare a 50 mg/mL suspension by mixing 10 aliquots of alectinib with 10 mL of olive oil, dispersing 7 150 mg capsules of the drug in each of them. Blend the 10 aliquots and add olive oil until a final volume of 210 mL is obtained[12,13]. Method 2: Disperse 150 mg capsules in 40 mL of warm water[13].	Method 1: Tested for feeding route administration. The stability of the product has not been determined. Method 2: Information available for feeding tube administration. Stable for 6 hours at 25 °C. Dispersion in water may result in clogging of the feeding tube.
ANAGRELIDE hard capsules (Xagrid®, GD)	No information available.	
AXITINIB film-coated tablets (Inlyta®)	Dissolve tablets in 15 mL of water[14].	Use an amber syringe or avoid direct sunlight exposure.
BEXAROTENE soft capsules (Targretin®)	Prepare a 1 mg/mL oral suspension. To do that, Split the 75 mg capsule in half and wash the contents, suspending them in 75 mL of water[15].	
BICALUTAMIDE film-coated tablets (Casodex®, Probic®, GD)	Crush the tablet and add a small amount of water to form a paste. Add more water to bring the total volume to 15 mL and mix until any large particles are gone[13].	
BOSUTINIB film-coated tablets (Bosulif®)	No information available.	
BUSULFAN coated tablets (Busulfan Aspen®)	Method 1 (preferred): Prepare a 2 mg/m suspension: Crush 50 2 mg tablet and dissolve in 50 mL of simple syrup[13,15-17]. Method 2: Crush the tablets and disperse in water[13,15].	Foreign drug. Method 1: Store in an amber jar. Stable for 30 days if refrigerated. Method 2: Tested for feeding tube administration. No data on stability.
CABOZANTINIB film-coated tablets (Cabometyx®)	No information available.	
CAPECITABINE film-coated tablets (Xeloda®, GD)	Dissolve 4 500 mg tablets in 200 mL of warm water and shake for 15 min until dissolution[15,18].	
CYCLOPHOSPHAMIDE coated tablets (Genoxal®)	Crush to fine powder, Disperse in 20 mL of water[15,19].	Tablets may be crushed but the manufacturer recommends preparing the oral liquid form using the powder for injectable solution[15].
CYCLOPHOSPHAMIDE powder for solution for injection and infusion (Genoxal®)	Method 1: Reconstitute a 1g vial with 25 mL of saline solution. Then mix with simple syrup or Ora-Plus® in a 1:1 proportion to obtain a 20 mg/mL suspension[15,20]. Method 2: Reconstitute the 1 g vial with 50 mL of saline solution. Then mix with simple syrup or Ora-Plus® until a final volume of 100 mL is obtained to achieve a 10 mg/mL suspension[15,21].	Store in a syringe or amber glass jar. Stable for 56 days if refrigerated, for 8 days at room temperature if formulated with simple syrup, or for 3 days at room temperature if formulated with Ora-Plus®.
CHLORAMBUCIL film-coated tablets (Leukeran®)	Method 1 (preferred): Crush 60 tablets with a mortar and pestle, add 30 mL of methylcellulose, and simple syrup until a final volume of 60 mL is obtained[15]. Method 2: Use a tablet dispersion technique[19].	Foreign drug. Method 1: Protect from sunlight and keep refrigerated. Shake vigorously before use. Stability: 7 days.
COBIMETINIB film-coated tablets (Cotellic®)	No information available.	
CRIZOTINIB hard capsules (Xalkori®)	Dissolve the capsules in hot water (50 °C), without crushing[22].	Tested for feeding tube administration.
DABRAFENIB hard capsules (Tafinlar®)	Not recommended by the manufacturer on account of the agent's chemical instability[20]. No additional information is provided.	Available as a foreign drug: 10 mg orodispersible tablet (pediatric dosage form).

Table 1 *(cont.).* Overview of the administration of oral antineoplastics in patients with deglutition disorders

Drug	Dosage form modifications*	Remarks
DASATINIB film-coated tablets (Sprycel®)	Method 1 (preferred): Prepare a suspension by adding the necessary tablets to 30 mL of 100% orange or apple juice (with no preservatives) and let stand. After 5, 15 and 20 min shake for 3 seconds while making circular movements[13,15]. Method 2: Disperse the tablet in 10 mL of water, shaking every 5 minutes (15 minutes in all)[13].	Method 1: Tested for feeding tube administration. Must be dissolved in orange juice as water interferes with product's bioavailability. Method 2: No data on stability.
ENZALUTAMIDE film-coated tablets (Xtandi®)	No information available.	
ERLOTINIB film-coated tablets (Tarceva®, GD)	Method 1 (preferred): Crush the medication in a mortar and pestle and add the resulting powder to a 1:1 mixture of Ora-Plus® and Ora-Sweet® to obtain a 10 mg/mL suspension[23]. Method 2: Dissolve a tablet in 15 mL of water[13]. Method 3: Dissolve the drug in a glass with 100 mL of water and shake the contents for 8 minutes[19].	Method 1: Store in an amber plastic jar. Stable for 28 days at 25 °C. Method 2: Tested for feeding tube administration. Method 3: As a precautionary measure, do not crush los tablets and do not let the suspension stand.
ESTRAMUSTINE hard capsules (Estracyt®)	Open the capsule and disperse in 15 mL of water[19,24].	
ETOPÓSIDE soft capsules (Vepesid®)	No information available.	
ETOPOSIDE concentrate for solution for infusion (Etopósido Teva®)	Extract the dose from a 30 mg/mL etoposide vial and dilute with saline solution until a 10 mg/mL suspension is obtained[13,25,26].	Store in an oral syringe or an amber jar. Stable for 22 days at room temperature[13,25,26]. To mask its bitter taste, the solution may be diluted in apple juice, orange juice or lemonade just before its administration to a concentration < 0.4 mg/mL[26].
EVEROLIMUS tablets (Afinitor®, Votubia®, GD)	According to the manufacturer, the tablets can be dispersed in a glass with 30 mL of water, stirring the contents until complete dissolution (7 minutes)[27].	The manufacturer does not recommend crushing or chewing the tablets[28].
EVEROLIMUS dispersible tablets (Votubia®)	Must be taken as a suspension, using water as a vehicle[27].	Use an oral syringe or a small glass. Votubia® 2 mg, 3 mg and 5 mg dosage forms are dispersible tablets.
FLUDARABINE coated tablets (Beneflur®)	No information available.	
GEFITINIB film-coated tablets (Iressa®, GD)	No crushing, dissolve the tablet in half a glass of water, stirring from time to time (for up to 20 minutes)[29].	May be administered through the nasogastric or gastrotomy route.
HYDROXYCARBAMIDE hard capsules (Hydrea®)	Method 1 (preferred): Disperse the contents of 20 capsules in 50 mL of water at room temperature. Shake for several hours. Filter the solution to remove insoluble excipients, and add 50 mL of flavored syrup to obtain a final concentration of 100 mg/mL[15]. Method 2: Open the necessary capsules. Disperse the contents in a glass of water[30]. Method 3: Open and disperse in 20 mL of water[19].	Method 1: Store in an amber plastic jar. Stable for 3- 9 months at room temperature. Do not use hot water as it reduces the product's chemical stability. Method 2: Some insoluble excipients could remain on the surface. Method 3: Specific to feeding tube administration.
IBRUTINIB capsules (Imbruvica®)	Open the capsules, Disperse the contents in water[31,32].	Tested for nasogastric or gastrotomy feeding.
IBRUTINIB film-coated tablets (Imbruvica®)	The product's label recommends not to break or chew the tablets. No additional information available.	
IDELALISIB film-coated tablets (Zylelig®)	No information available.	
IMATINIB film-coated tablets (Glivec®, GD)	Method 1 (preferred): Crush and mix with Ora-Sweet® until a 40 mg/mL suspension is obtained[23]. Method 2: Dissolve los tablets in a glass of 200 mL of water or apple juice (50 mL for 100 mg tablets and 200 mL for 400 mg tablets). Shake until dissolution[33,15].	Method 1: Stable for 14 days if stored in amber plastic jars at 25 °C and 4 °C.

Table 1 *(cont.).* Overview of the administration of oral antineoplastics in patients with deglutition disorders

Drug	Dosage form modifications*	Remarks
IMATINIB hard capsules (GD)	The contents of the capsules may be dispersed in a glass of mineral water or apple juice[34].	
LAPATINIB film-coated tablets (Tyverb®)	Crush the tablets and dissolve the resulting powder in a 1:1 mixture of Ora-Plus® y Ora-Sweet® to obtain a 50 mg/mL suspension. Shake for 15 minutes[23].	Store in a amber plastic jar. Stable for 28 days, at 25 °C.
LENALIDOMIDE hard capsules (Revlimid®)	Disperse the whole (unopened) capsule in hot water (55 °C)[35,13].	Crystal vial or syringe. Stable in hot water for 24 hours. Tested for the gastrotomy route.
LENVATINIB hard capsules (Lenvima®, Kisplyx®)	Dissolve the whole (unopened) capsules, without opening them. Let stand in water or apple juice for 10 minutes. Then shake for at least 3 minutes[36,13].	Stable for 24 hours. Tested for nasogastric tube administration.
LOMUSTINE capsules (CeeNU®)	Open the capsules and disperse the contents in a small amount of orange juice, yoghurt or icecream[37].	Foreign drug.
MELPHALAN film-coated tablets (Alkéran®)	Method 1: Not recommended[15]. Method 2: A Tablet dispersion technique should be used[19].	Foreign drug. Method 1: When prepared in methylcellulose, simple syrup or cherry syrup is dissolves rapidly[15]. Method 2: Recommended for feeding tube administration.
MERCAPTOPURINE tablets (Mercaptopurina Silver®)	Method 1 (preferred): Crush 30 tablets, add 5 mL of water, and shake to form a paste. Subsequently, add 10 mL of simple syrup and cherry syrup to a final volume of 30 mL, to obtain a 50 mg/mL suspension[15,38]. Method 2: Crush 10 tablets and add them to a 1:1 mixture of Ora-Plus® and Ora-Sweet®. Geometric dilution should be allowed until a final volume of 100 mL is obtained[39,40]. Method 3: Use a Tablet dispersion technique, with 10 mL of water[19].	Method 1: Store in an amber glass jar. Shake thoroughly before use. Stable for 5 weeks at room temperature. Addition of 0.1% ascorbic acid increases the product's shelf life to 11 weeks at room temperature. Method 2: Store in a plastic or glass jar at room temperature. Method 3: Recommended for tube feeding. No data on stability.
METHOTREXATE tablets (Metotrexato WYETH®, GD)	Disperse the tablets in 10 mL of water, shake until complete dissolution[13, 19].	The solution should be prepared directly from the vial.
METHOTREXATE injectable solution (WYETH®, GD)	Method 1 (preferred): Add 20 g of sodium bicarbonate to 250 mL of cherry syrup and top up with distilled water q. s. 1,000 mL. Add 80 mL of methotrexate from the 25 mg/mL vial to obtain a 2 mg/mL suspension[41]. Method 2: Mix 250 mL of cherry syrup, add 20 g of sodium bicarbonate and then add chloroformic water q. s. 1,000 mL. Extract 1.6 mL from the 25 mg/mL methotrexate vial and bring the total volume to 20 mL with the previously prepared solution to obtain a 2 mg/mL suspension[15].	Store in an amber or clear glass jar. Stable for 1 month if refrigerated or kept at room temperature. No bioavailability, C_{max} or AUC differences have been observed between tablets and the oral solution.
MIDOSTAURIN soft capsules (Rydapt®)	No information available.	
MITOTANE tablets (Lysodren®)	Crush the tablets and dissolve in MCT oil; each granule is dissolved in MCT oil. The solution must be added to some fat-rich food such as milk, chocolate milk drink or yoghurt[42].	
NILOTINIB hard capsules (Tasigna®)	The contents of the capsules can be dispersed in a spoonful of apple compote[43].	No more than one spoonful of apple compote or food other than apple compote should be used.
NIRAPARIB hard capsules (Zejula®)	No information available.	
OLAPARIB film-coated tablets (Lynparza®)	Not recommended.	The manufacturer advises against crushing/ dissolution of the tablets due to a potential decrease in efficacy.
OLAPARIB hard capsules (Lynparza®)	Not recommended.	The manufacturer advises against crushing/ dissolution of the product due to a potential decrease in efficacy.
OSIMERTINIB film-coated tablets (Tagrisso®)	Disperse in 50 mL of still water, without crushing. Shake until fully dispersed. In the event of administration through nasogastric intubation, the tablet may be dispersed in 15 mL of water[44].	

Table 1 *(cont.).* Overview of the administration of oral antineoplastics in patients with deglutition disorders

Drug	Dosage form modifications*	Remarks
PALBOCICLIB hard capsules (Ibrance®)	Dissolve the capsules in hot water and shake vigorously for at least 4 minutes. Let stand for 10 minutes and mix the suspension again several times by inversion[13].	Stable for 2 hours at room temperature if stored in a syringe. Recommended for nasogastric intubation (≥ 8 Fr) and gastrostomy.
PAZOPANIB film-coated tablets (Votrient®)	Add 25 tablets to 25 mL of water and let stand until the tablets start disintegrating. Stir until a paste is formed and add Ora-Sweet® by geometric dilution until a 100 mL volume is obtained. Blend the suspension making circular movements (do not shake to prevent foam formation)[45,46].	Store in an amber glass jar. Mix by making circular movements for 30 seconds before dosing. Stable for 35 days if kept refrigerated. Tested for nasogastric intubation.
POMALIDOMIDE hard capsules (Imnovid®)	Obtain a suspension by dispersing the contents of the capsule in water (2 mg in 75 mL)[47].	140 mL of water must be administered immediately afterwards.
PONATINIB film-coated tablets (Iclusig®)	No information available.	
PROCARBAZINE capsules (Natulan®)	Method 1 (preferred): Open 10 capsules and add 2 mL of glycerin. Mix until a paste is formed. Finally, perform a geometric dilution with 50 mL strawberry syrup until a 10 mg/mL suspension is formed[15]. Method 2: Open and disperse in 20 mL of water[19].	Method 1: Store in an amber glass jar. Method 2: Recommended for intubated patients.
REGORAFENIB film-coated tablets (Stivarga®)	No information available.	
RIBOCICLIB film-coated tablets (Kisqali®)	No information available.	
RUXOLITINIB tablets (Jakavi®)	Dissolve each tablet in 40 mL of water and shake for 10 minutes[13].	Should be administered within 6 hours from preparation. Recommended for nasogastric intubation (≥ 8 Fdar).
SORAFENIB film-coated tablets (Nexavar®)	Dissolve 2 tablets in 60 mL of water and let stand. After 5 minutes start stirring until the tablets start to disperse and a fine suspension is formed (it takes 5 more minutes)[15].	Remnants of the biofilm may show up in the suspension, but this has no significance.
SUNITINIB hard capsules (Sutent®)	Method 1 (preferred): Open and disperse the contents of the capsules in a 1:1 mixture of Ora-Plus® and Ora-Sweet®, to obtain a 10 mg/mL suspension. The suspension will be viscous and must be thoroughly shaken[48]. Method 2: Open the capsule and add the contents of each capsule to a spoonful of apple compote or yoghurt at room temperature. Repeat the process for each capsule[49]. Method 3: The contents of the capsules (up to 750 mg) may be mixed with 75 mL of apple juice[15].	Method 1: Must be stored in an amber plastic jar. Stable for 60 days at room temperature or if kept refrigerated at 4 °C. Method 2: Administered within 30 minutes. Drink 60 mL of water or apple juice following administration. Method 3: Administer within 2 hours.
THALIDOMIDE hard capsules (Talidomida Celgene®)	Open and disperse the contents of the capsules in 20 mL of water[19].	Foreign drug. Recommended for intubated patients.
TEMOZOLOMIDE hard capsules (Temodal®, GD)	Method 1 (preferred): Mix the contents of ten 100 mg capsules with 500 mg Povidone K-30 powder. Crush and mix until a fine powder is obtained. Add 25 mg of anhydrous citric acid dissolved in 1.5 mL of water and mix to form a paste. Add 50 mL of Ora-Plus® and mix. Subsequently add Ora-Sweet® or Ora-Sweet SF® until a final volume of 100 mL is obtained. Shake vigorously to obtain a 10 mg/mL suspension[50]. Method 2: Open and disperse the contents of the capsule with 20 mL of orange juice[19].	Method 1: Store in an amber plastic jar. Shake vigorously before use. Stable for 60 days if refrigerated at 4 °C. Do not store at room temperature for longer than a week if prepared with Ora-Sweet®, or for more than 2 weeks if prepared with Ora-Sweet SF®. Method 2: recommended for intubated patients.
THIOGUANINE tablets (Lanvis®)	Crush 15 tablets and add 15 mL of Ora-Plus® and Ora-Sweet®. The amount must be enough for 30 mL[51].	Foreign drug.
TOPOTECAN hard capsules (Hycamtin®)	Open, disperse in 20 mL of water, and administer[19].	Recommended for intubated patients.
TRAMETINIB film-coated tablets (Mekinist®)	No information available.	

Table 1 *(cont.).* Overview of the administration of oral antineoplastics in patients with deglutition disorders

Drug	Dosage form modifications*	Remarks
TRAMETINIB powder for oral suspension (Mekinist®)	Follow the instructions of the product's label.	Foreign drug.
TRETINOIN soft capsules (Vesanoid®)	Method 1 (preferred): Introduce the capsules into 10 mL of distilled water at 45 °C, together with 5 mL of mineral oil, in a 20 mL syringe. Shake vigorously until complete dissolution (more than 5 minutes)[52]. Method 2: Dissolve the soft capsules in 20 mL of sterile water at 37 °C[53].	Method 1: Protect from sunlight. Stable for 24 hours. Tested for tube feeding. Method 2: Tested por nasogastric intubation.
TRIFLURIDINE/TIPIRACIL film-coated tablets (Lonsurf®)	No information available.	
VANDETANIB film-coated tablets (Caprelsa®)	Disperse the tablets in half a glass of non-carbonated water, without crushing. Stir until complete dispersion (10 minutes)[54].	Other liquids should not be used. May be administered through a nasogastric or gastrotomy tube.
VEMURAFENIB film-coated tablets (Zelboraf®)	Dissolve a Tablet in 15 mL of water[55].	Vemurafenib is virtually insoluble in water but tablets are formulated microprecipitate, which increases solubility. Tested for nasogastric intubation.
VENETOCLAX film-coated tablets (Venclyxto®)	No information available.	
VINORELBINE soft capsules (Navelbine®, GD)	The manufacturer recommends not to manipulate the product. Not recommended for feeding tube administration[19]. No additional information available.	
VISMODEGIB hard capsules (Erivedge®)	Disperse the capsule in 50 mL of warm water[13].	Tested for gastrotomy feeding.
VORINOSTAT capsules (Zolinza®)	Dissolve the contents of 20 capsules in 20 mL of Ora-Plus® and shake to homogenize the mixture. Add Ora-Sweet® until a final volume of 40 mL is obtained and shake to obtain a 50 mg/mL suspension[15].	Foreign drug. Store in an amber or clear glass jar.

AUC: area under the plasma drug concentration-time curve; C_{max}: maximum concentration; GD: generic drug; MCT: medium chain triglycerides; q. s.: quantum statis (sufficient amount for).

*Manipulation of antineoplastics must be performed in accordance with the relevant guidelines on the handling of hazardous drugs. Preparation of oral antineoplastics must be carried out in a class 1 biological safety cabinet using the required personal protection equipment (double gloves, fluid-resistant gowns, and facemasks). Wearing of simple gloves is recommended for administration of solid oral antineoplastics, whereas double gloves and a gown should be worn for administering the liquid form of the drug. Protective eyewear should be worn when there is a risk of splatter. Respiratory protective equipment should be donned to prevent inhalation of hazardous substances[56-58].

A review on the preparation and administration of oral antineoplastics by the enteral route was recently published in the United States. However, this review includes several drugs that are not available in Spain and makes no mention of the antineoplastics most frequently used in our clinical practice[13].

Modification of dosage forms to adapt them for administration to patients with dysphagia could result in changes in the drugs' bioavailability profile, with a potential decrease in their therapeutic effect[59]. As shown in table 1, in some cases it is necessary to change the formulation or take into consideration a series of factors to ensure the quality of the treatment administered to the patient. For that reason, the lack of information and the insufficient training in the preparation and administration of medications to patients with dysphagia often compromises the safety and effectiveness of treatment. Indeed, it is not unusual for formulations not amenable to manipulation to be modified, often without due consideration of criteria such as compatibility with other drugs or nutritional products, or with the vehicle they are diluted in[60-62].

In patients with swallowing difficulties, whether or not on an enteral feeding tube, recourse to preparation and administration methods often not contemplated in the drugs' labels may be warranted provided that such methods are supported by studies dealing specifically with the medication in question. In cases where there is no information on the subject, a case-by-case analysis is required that takes into consideration the risk/benefit balance and the available therapeutic alternatives.

It should be underscored that manipulation of oral antineoplastics must be carried out in accordance with the available guidelines on the handling of hazardous drugs[56-58]. Moreover, that administering drugs through feeding tubes requires observance of a series of general recommendations such as not mixing the drug in question with other medications or with enteral nutritional support products; and washing the tube with 15 ml of water before and after administration[13].

The main limitation of this review is the scarce information found about the manipulation of antineoplastic drugs, both in the products' labels and in other sources reviewed. Furthermore, the evidence that does exist is of low quality. For that reason, it is essential to conduct further research in this field, leading to stability and pharmacokinetic studies that allow a more informed administration of oral antineoplastics in patients with swallowing disorders.

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Contribution to the scientific literature

Although administration of oral antineoplastics in patients with deglutition disorders is garnering growing amounts of interest, information about the subject is extremely scarce. This study consisted in a review of the available literature, which served as a bases to prepare an easy reference guide to the preparation and administration of oral antineoplastic treatment in this group of patients.

The present review therefore contributes to facilitating access to the information available on the preparation and administration of the oral antineoplastics available in Spain to patients with dysphagia, whether or not on a feeding tube, in order to improve their safety and help them achieve their therapeutic goals.

The information provided is of particular interest to physicians, pharmacists, and nurses as it will contribute to improving the management of cancer patients with swallowing disorders.

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