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REVIEW ARTICLE

Preparation of extemporaneous solutions with chemotherapeutic agents for pediatric patients: Ensuring safe and effective treatment

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ABSTRACT

The treatment of pediatric oncology patients involves the use of specialized drugs adapted to their specific needs, thus, in view of the need for pharmacotherapeutic follow-up with oral dosage forms (ODF), in the unavailability of liquid formulations, a strategy is the preparation of extemporaneous solutions from the manipulation of tablets and capsules added to liquid vehicles (eg: water, simple syrup) adjusting palatability and facilitating access. This review article will serve as a guide, providing information on the preparation, stability and storage of extemporaneous oral chemotherapy formulations (tablets, capsules, injection powder or injection solution) for use in clinical practice, with the aim of promoting adherence to treatment linked to safety and effectiveness, based on good handling practices and occupational risk. The results of this review are summarized in a table and based on a composition of the cited documents, tests carried out and the authors' judgment on all the data collected. Twenty drugs were identified as potentially important for clinical practice. Strategies for preparing extemporaneous solutions of chemotherapeutic agents for pediatric patients require more scientific data or even publications of adaptations used. Even with the scarcity of data for some drugs, this review covers the most trivial drugs in clinical practice, including information on preparation, warning about stability and storage, and also included relevant guidelines on the mode of administration in view of the adherence and effectiveness of the drug. The professional who handles these cytotoxic drugs needs to understand from pharmacotechnical aspects and guard against exposure in the preparation, so that he can continue to guarantee access and adherence to treatment and follow rigorous literature and protocols, implementing the best practices and providing adequate, effective, and personalized treatment.

Keywords: extemporaneous formulations, oral antineoplastic agentes, extemporaneous preparation for children, medication administration through enteral feeding, stability and bioavailability.

Introduction

Cancer treatment involves the use of injectable drugs, linked to a high complexity and the follow-up of long-term treatment, with oral dosage forms (ODF). However, a large part of the therapeutic arsenal consists of capsules and tablets, narrowing the dosage and access to the drug, mainly for pediatric patients, patients using enteral tubes or gastrostomy, those unable to swallow due to some clinical condition, for example in duration of mucositis and dose adjustment by body surface.

The treatment of pediatric oncology patients involves the use of specialized drugs adapted to their specific needs, thus, in view of the need for pharmacotherapeutic follow-up with ODF, in the unavailability of liquid formulations, a strategy is the preparation of extemporaneous solutions from the manipulation of tablets and capsules added to liquid vehicles (eg: water, simple syrup) adjusting palatability and facilitating access.

However, this tactic requires pharmacotechnical information, based on evidence about stability, storage conditions, packaging and manipulation technique. Processes that can limit the preparation of extemporaneous solutions and the occupational risk inherent to the chemotherapeutic agents that the professional is exposed to, must also be considered.[1,2]

After preparing the solution, pharmacotherapeutic follow-up by a multidisciplinary team, promotes continued access to the medication, contributing to the assessment of adherence to treatment, which integrates efficacy through the feasibility of a safe strategy. Therefore, it is necessary for the professional to dedicate himself to the preparation, considering risks of contamination, dosage calculation (eg: parts/volume - w/v) and formulation failure, thus articulating with principles of good handling practices.[3]

This review article will serve as a guide, providing information on the preparation, stability and storage of extemporaneous oral chemotherapy formulations (tablets, capsules, injection powder or injection solution) for use in clinical practice, with the aim of promoting adherence to treatment linked to safety and effectiveness, based on good handling practices and occupational risk.

Materials and methods

Systematic review comprising tertiary resources, drug manufacturers, and primary literature was performed to identify information related to extemporaneous composition or alternative routes of administration for a predetermined list of oncology drugs.

A search was carried out observing publications available in Medline (Medical Literature Analysis and Retrieval System Online), LILACS - BVS (Latin American and Caribbean Literature in Health Sciences – Virtual Health Library) and SciELO (Scientific Electronic Library Online).

PubMed literature (May 19 to August 10, 2023), for studies in Portuguese and English, by generic name of the identified drugs and the following search terms: “extemporaneous formulations”, “oral antineoplastic agentes”, “extemporaneous preparation for children”, “medication administration through enteral feeding”, “stability and bioavailability”.

After reading abstracts of the collected papers, only articles containing the preparation method, materials and stability studies of extemporaneous solutions from forms commercially available were selected.

Results

The results of this review are summarized in a table and based on a composition of the cited documents, tests carried out and the authors' judgment on all the data collected. Twenty drugs were identified as potentially important for clinical practice.

Table 1: Summary of extemporaneous oral liquid preparation of oral oncology drugs and stability.

Drug	Dosage forms	Extemporaneous Oral Liquid Formula	Concentration	Storage and stability	Comments
Capecitabin [4]	Coated tablet: 500 mg	Macerate 37 capecitabine tablets (500 mg). Mix the powder obtained with 92.5mL of Ora plus [a] and 92.5 mL Ora Sweet [b]. Stir the mixture for 15 minutes until completely	100 mg/mL	Store under refrigeration at 2ºC to 8ºC for up to 14 days.	Administer with a meal. The solution may also be administered through a NGT or other enteral tube.
Cyclophosphamide [5]	Extemporaneous powder (for preparation before use) for injection.	Reconstitute 1000 mg of powder with 50 mL of water for injection. Mix the entire contents of the bottle with 50 mL of simple syrup (sufficient quantity to 100 mL).	10 mg/mL	Store under refrigeration at 2ºC to 8ºC for up to 56 days.	After reconstituting the powder, shake the bottle well until completely dissolved.
Dasatinib [6]	Coated tablet: 20 mg or 50 mg	Add 30 mL of cold orange or apple juice, without preservatives, to the prescribed dose. Let it dilute without stirring. After 5 minutes, mix the contents for 3 seconds and repeat the process every 5 minutes until the tablet is completely dissolved. Mix one last time and administer immediately.	Dose dependent.	Intended for immediate use.	Administer separately from antacids. At least 2 hours before or after an antacid.
Erlotinib [7]	Tablet: 150 mg	Macerate a tablet and dilute powder in 15 mL of Ora Plus [a] or Ora Sweet [b].	10 mg/mL	Store at 25ºC for a maximum of 28 days.	Sedimentation of the solution may occur, easily reversed by gently shaking the bottle.

Drug	Dosage forms	Extemporaneous Oral Liquid Formula	Concentration	Storage and stability	Comments
Etoposide [6]	Injectable solution 20 mg/mL	Dilute the required dose in 0.9% sodium chloride, in a 1:1 ratio. Final concentration 10 mg/mL. This dilution can be carried out in an oral pack syringe.	10 mg/mL	22 days at room temperature (15° to 25° C) regardless of lighting conditions.	Store in oral pack syringe or amber bottle. Concentration of 1mg/mL has acceptable stability when administered in orange juice, apple juice and lemonade or syrup. Showing loss of less than 1% after 3 hours.
Everolimus [8]	Tablets: 2,5 mg, 5 mg or 10 mg	Disperse tablet in ~30 mL of water; gently stir.	Dose dependent	Intended for immediate use	None
Hydroxyurea [10,11]	Capsule: 500 mg	Remove the contents of 20 capsules and transfer them to an amber bottle with a capacity of 100 mL. Add enough to 100 mL of simple syrup.	100 mg/mL	28 days at room temperature (15° to 25 ° C).	1 hour of fasting before and after administration of the solution. The addition of flavorings is recommended to mask the taste of
Imatinib [9]	Tablets: 100 mg or 400 mg	Whole tablets can be diluted in a glass of water or apple juice (50 mL for the 100 mg tablet, and 200mL for the 400mg tablet). Mix until the tablet is completely dissolved.	2 mg/mL	Intended for immediate use	Separate a glass to carry out these dilutions. Do not mix with other utensils.
Isotretinoin [12]	Capsule: 10 mg or 20 mg	Pierce the capsule and dilute the contents in olive oil.	Dose dependent.	72 hours at room temperature (15° to 25°C)	As it is lipophilic, it can be administered without leaving traces on the wall of the cup used, which reduces the risk of contamination.
Lomustine [13]	Tablets: 10 mg or 40 mg	Empty contents of 20 capsules of lomustine 10 mg into a small plastic med cup. Add 10 mL of simple syrup and mix well. Withdraw the lomustine suspension into an amber oral syringe. Add more simple syrup until complete 20 mL. Cap syringe or transfer to a amber vial. Note: Quantities may vary according to the prescribed dose.	10 mg/mL	Intended for immediate use	Administering on an empty stomach may reduce the incidence of nausea and vomiting.
Mercaptopurine [15,16]	Tablet: 50 mg	Method 1: Crush the tablets and mix with 1% methylcellulose with parabens (10 mL) + simple syrup, sufficient quantity for 100 mL.	5 mg/mL	56 days at room temperature (15° to 25°C) or 90 days under refrigeration (2° to 8°C).	Shake well before using.
	Tablet: 50 mg	Method 2: Crush the tablets and mix with 35 mL of 2% methylcellulose (35 ml) + 2 mL of 95% alcohol + 22 mL of cherry syrup + simple syrup, sufficient amount to 100 mL.	50 mg/mL	14 days at room temperature (15° to 25°C).	Shake well before using.
Methotrexate [13]	Injectable solution 25 mg/mL	Method 1: Dissolve sodium bicarbonate 0.6 g in sterile water in a mortar or in a beaker. Add 7.5 mL of Ora Sweet [b] slowly. While continuing to stir, add 2.4 mL of methotrexate for injection 500 mg/20 mL injectable solution. Note: do not use methotrexate powder for injection. Add sufficient sterile water to reach a final volume of 30 mL (2 mg/mL).	2 mg/mL	Stable for 120 days at room temperature (15° to 25°C) or under refrigeration (2° to 8°C), in a amber glass bottle.	No significant difference in bioavailability between extemporaneous oral solution and comercial oral tablet.
		Method 2: Tablet may be added into a syringe and suspended in water.	Dose dependent	Intended for immediate use	None
Mitotane [14]	Tablet: 500 mg	Formation of microemulsion with an oil, a surfactant and cosurfactant in the same proportion. (1:1:1) Capryol® 90 [c] / Tween® 20 [d] /Cremophor® [e]	Dose dependent	Clear and transparent microemulsion stable for 3 days at room temperature (15° to 25°C).	Administration with milk or chocolate increases plasma mitotane levels.
Pazopanib [17]	Coated tablet: 200 mg or 400 mg	Macerate 5 g of Pazopanib + 25 mL sterilized water + sufficient quantity for 100 mL of Ora-Sweet [b].	50 mg/mL	35 days under refrigeration (2° to 8°C)	Concomitant administration with a meal increases AUC and Cmax by two times. Therefore, it is necessary at least 1 hour before or 2 hours after the meal.
Sorafenib [18]	Coated tablet: 200 mg	Macerate 4 tablets of Sorafenib 200 mg, until it forms a fine powder with flakes of red film and add a 1:1 mixture of Ora Sweet® [b]: Ora Plus® [a], sufficient quantity for 16 mL.	50 mg/mL	Intended for immediate use	The concentration can be adjusted according to dose needs. Administer 1 hour before or 2 hours after eating. Do not take antacids and gastric protectors concomitantly.
Tamoxifen [13]	Coated tablet: 10 mg or 20 mg	Place two 10 mg tablets in 40 ml of water and let it rest. Mix until the tablets are completely disintegrated to form a particular fine suspension. (Dispersaltime for the 10 mg tablet is 2 to 5 min.)	Dose dependent.	Intended for immediate use	Commercial solution 10 mg/5 mL, available for import to countries that do not have this pharmaceutical form.
Temozolamide [6,19]	Capsules: 5 mg, 20 mg, 100 mg, 140 mg, 180 mg or 250 mg	Mix the contents of 10 capsules (100 mg each) and 500 mg of povidone K-30 powder in a glass mortar. Add 25 mg anhydrous citric acid dissolved in 1.5 mL purified water and mix to a uniform paste. Mix while adding 50 mL Ora-Plus® [a] in incremental proportions. Transfer to an amber plastic bottle. Rinse mortar 4 times with small portions of either Ora-Sweet® [b], and add quantity of Ora-Sweet® [b] sufficient to make 100 mL (10 mg/mL).	10 mg/mL	Stable for 7 days at room temperature or for 60 days under refrigeration (preferred).	Suspension may have pinkish color when refrigerated or may appear darker when stored at room temperature.
Thioguanine [6,19,21]	Tablet: 40 mg	Method 1: Crush fifteen 40 mg of Thioguanine and transfer to syringe. Add 7,5 mL of sterile water, snake for 1 minute and after 2 minutes shake again. After this, add a mixture of ORA-Plus® [a]: ORA-Sweet® [b](1:2), to a final volume of 30 mL. Transfer to a amber vial.	20 mg/mL	Stable for 90 days refrigerated.	Label "shake well" and "refrigerate".
	Tablet: 40 mg	Method 2: An oral suspension may be made with tablets, Methylcellulose 1% and a simple syrup. Crush fifteen 40 mg tablets and reduce to a fine powder. Add 10 mL methylcellulose 1% in	20 mg/mL	Stable for 84 days refrigerated (2° to 8°C) (preferred) or at room temperature. (15° to 25°C)	Label "shake well" and "refrigerate"
Topotecan [13,22]	Injectable solution 1 mg/mL	Reconstituted topotecan solution for injection (1 mg/mL concentration) may be mixed with up to 30 mL of acidic fruit juice (eg, apple, orange, grape).	Dose dependent.	Intended for immediate use.	None
Tretinoin (ATRA) [6,20]	Capsule (Soft gelatin): 10 mg	Method 1: Place capsule(s) in a medicine cup or small bowl, and add ATRA 10 mg warm (~37°C or 97°F) water or warm milk to cover the capsule(s). Wait 2–3 min until capsule is soft, then drink milk or water with the softened capsule, or swallow the softened capsule.	Dose dependent.	Intended for immediate use.	Tretinoin has also be administered sublingually by squeezing the capsule contentes beneath the tongue.
	Capsule (Soft gelatin): 10 mg	Method 2: Place daily dose of ATRA in a sterile 50-ml tube. Add 20 ml of sterile water, then heat the tube in a water bath to 37°C until the capsules melt and the suspension is liquefied. The resulting fluid is administered by nasogastric tube.	Dose dependent.	Intended for immediate use.	Cut the capsule with a double layer of glove.
	Capsule (Soft gelatin): 10 mg	Method 3: Dissolve in 10mL of distilled water (45 ◦C), and 5mL of mineral oil was added to work as a lipophilic carrier. A 5 mL dead space was left inside a 20 mL. Shake the mixture well until the entire coat dissolved.	Dose dependent.	Intended for immediate use.	Plasma concentration may be altered.

NOTES: a) Ora-Plus® is an oral suspending vehicle that accepts dilution of up to 50% or more with water, flavoring agents, or syrups while still retaining its suspending properties. It has a pH of approximately 4.2. b) Ora-Sweet® syrup vehicle is a flavoring vehicle for oral extemporaneous preparations. Contains glycerin and sorbitol to prevent "cap lock," a problem associated with many syrups. Ora-Sweet is buffered to a pH of about 4.2. c) Capryol 90® - A nonionic water-insoluble surfactant used as a cosurfactant in the oral lipid-based formulation. d) Tween® 20 - O/W emulsifier, solubilizing agent, and wetting agent. e) Cremophor® - Non-ionic solubilizer and emulsifier that is made by reacting ethylene oxide with castor oil.

Discussion

The preparation of extemporaneous solutions of chemotherapy agents requires good handling practices, linked to the scientific basis of the pharmacotechnical feasibility of handling the medication without altering its pharmacological properties. In this sense, several studies [6,13,23,24] were verified, which compiled data on these adjustments and others that report clinical cases presenting the possibility of adapting pharmaceutical forms for pediatric oncology patients.

The difficulty of data related to adaptation to an alternative route is added to the attention to considering specific properties of the drug since

the formulation that carries the medicine cannot interfere with the pharmacological action or even the effectiveness. In this sense, excipients such as binders (Ex: Croscarmellose, Starch) coordinate the release of the drug in tablets, which when these same binders are macerated, can interfere with the formation of the solution by increasing the viscosity, or even making the stability of the adapted formulation unfeasible. Also, solubility in water must be considered, since some medications (Ex: Tamoxifen, Sorafenib) have a high Log P (Sorafenib: 3.96; Tamoxifen: 5.93) which can make it difficult to prepare an aqueous solution, not being viable, especially in terms of stability and homogeneity of the formulation. [25,26]

Therefore, we list points that must be considered in the strategy when preparing extemporaneous solutions: (1) Dose precision: Achieving an accurate dosage is crucial to avoid underdosing or overdosing in pediatric patients. Children's weight and age often fluctuate during treatment, requiring careful calculations to ensure the required dosage. (2) Drug stability: Oncology drugs can be sensitive to factors such as light, temperature and humidity. Extemporaneous manipulations must maintain physical-chemical stability throughout the period to guarantee therapeutic efficacy. (3) Compatibility: When combining drugs or additives to create an extemporaneous formulation, compatibility issues may arise, which may affect the effectiveness of the drug or lead to unwanted reactions. (4) Therapeutic Efficacy: carried out by therapeutic follow-up in clinical monitoring or even by serum dosage of the drug, sealing the process of formulating the extemporaneous solution.

Due to the scarcity of pharmacokinetic studies related to the medicines presented, the manipulation/administration of extemporaneous preparations, aligned with pharmaceutical experience related to the properties of medicines, and the regulatory aspects of each country, pharmacists can carry out research based on pre-clinical pharmacokinetics and then evaluate the relative safety of extemporaneous manipulation.

Furthermore, from the perspective of preparation through the handling of chemotherapy agents, the professional is exposed to the occupational risk of cytotoxicity. Therefore, following guidelines that provide for the mandatory use of individual and collective protective equipment, periodic monitoring in accordance with labor law, as well as controlling the time of exposure to these agents, are mandatory. In addition to the preparation for extemporaneous solutions, therapeutic follow-up, control of occupational risk, carrying out pharmacovigilance on potential adverse effects sometimes caused by a formulation adjuvant (e.g. coloring, flavoring) also needs to be included in the tactic of access to the medicine, covering from adherence, effectiveness and safety to treatment.

Professionals involved in the process of extemporaneous preparations, from prescription, handling, to administration, must be aware of the specific needs for handling chemotherapy drugs so that occupational health is valued, and family patients are properly guided. In the 70's, the National Institute for Occupational Safety and Health (NIOSH) was created, an agency focused on worker health, developing materials and projects to create safe and healthy workplaces. NIOSH's role has been to increase awareness of the health risks of working with hazardous drugs and to universally standardize precautions in handling hazardous drugs. This institute periodically publishes a list of dangerous medicines and guidelines for their handling, such as the use of certain individual and collective safety equipment. [27]

According to NIOSH, to consider a drug dangerous, the substance must present one or more of the following characteristics in humans or animals: carcinogenicity, teratogenicity, genotoxicity, reproductive toxicity and toxicity to organs and systems. Therefore, the handling of extemporaneous preparations of this type of substances requires specific care that must be considered, such as adequate infrastructure and protective equipment.[28]

This study has multiple limitations. The availability of data related to the extemporaneous compounding or administration of OODs that require manipulation of the commercial solid dosage form is not fully comprehensive. By the time this work is completed, other studies may have been published, or be under development with greater evidence of pharmacokinetic and pharmacodynamic data. These points were the authors' greatest concerns.

Due to these factors, this information is intended to be used as a tool in conjunction with other bioavailability data and clinical judgment to improve security practices.

Conclusion

Strategies for preparing extemporaneous solutions of chemotherapeutic agents for pediatric patients require more scientific data or even publications of adaptations used. Even with the scarcity of data for some drugs, this review covers the most trivial drugs in clinical practice, including information on preparation, warning about stability and storage, and also included relevant guidelines on the mode of administration in view of the adherence and effectiveness of the drug. The professional who handles these cytotoxic drugs needs to understand from pharmacotechnical aspects and guard against exposure in the preparation, so that he can continue to guarantee access and adherence to treatment and follow rigorous literature and protocols, implementing the best practices providing adequate, effective and personalized treatment.

Conflict of interest statement

The authors declare that there are no potential conflicts of interest or competing interests.

Consent for publication

All authors expressed their consent for the publication of this article.

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