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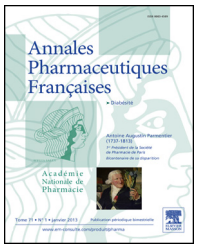

ORIGINAL ARTICLE

SFPO and ESOP recommendations for the practical stability of anticancer drugs: An update

Mise à jour des recommendations de la SFPO et de l'ESOP pour la stabilité pratique des anticancéreux

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Summary The recommandations for the practical stability of anticancer drugs published in 2010 by the French Society of Hospital Pharmacists (SFPO) and the European Society of Oncology Pharmacists (ESOP) have been updated. Ten new molecules have been included (asparaginase, azacitidine, bevacizumab, clofarabine, eribuline mesylate, folinate sodium, levofolinate calcium, nelarabine, rituximab, temsirolimus).

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MOTS CLÉS
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Dose banding ;
Stabilis®

Résumé Les recommandations concernant la stabilité pratique des préparations d'anticancéreux émanant de la Société française de pharmacie oncologique (SFPO) et de la Société européenne de pharmacie oncologique (ESOP) parue en 2010 ont été actualisées. Dix nouvelles molécules ont été ajoutées (asparaginase, azacitidine, bevacizumab, clofarabine, eribuline mesylate, folinate sodium, levofolinate calcium, nelarabine, rituximab, temsirolimus)

Introduction

These recommendations for storage conditions of anticancer drugs are the result of the deliberations of the SFPO (French Society for Oncology Pharmacy) stability group. The first edition of the data were published in 2008 by the Centre national hospitalier d'information sur le médicament, CNHIM — National Information Centre on Hospital Drugs. The stability group comprised Arnaud P, Astier A, Bellanger A, Bonan B, Breilh D, Burnel S, Daouphars M, Ferrio AL, Havard L, Helvig A, Husson MC, Pinguet F, Poisson N, Sarrut B, Vigneron J. These recommendations were adopted as the European standard by ESOP in 2010 and published in the European Journal of Oncology Pharmacy [1].

A new group with members of SFPO and European hospital pharmacists has updated this work in 2012. This new group comprised Alain Astier, Mikaël Daouphars, Frédéric Pinguet, Bertrand Pourroy, Jean Vigneron for SFPO and Jean Daniel Hecq from Belgium, Iben Larsson from Denmark and Rainer Trittler from Germany.

In this updated article, new drugs have been included (asparaginase, azacitidine, bevacizumab, clofarabine, eribuline mesylate, folinate sodium, levofolinate calcium, nelarabine, rituximab, temsirolimus). Some drugs received new informations (cisplatine, docetaxel, fludarabine, oxaliplatine, vincristine). Three drugs no longer available on the market have been removed from the table: chlormethine, mitoguazone and pirarubicine.

Selection criteria for the articles

New informations were selected by using the Stabilis database. For each monograph, the new publications until 2008 have been revised according to a checklist to select inclusion criteria for the physical and chemical stability. The articles were selected if they brought new informations for the daily practice (for example, extended stability for the preparation in advance). We decided to include the informations presented in posters if the stability study was in accordance to our criteria and submitted to publication. The stability data of simple solutions (one drug in one container) have been selected. The stability of mixtures or of non-injectable drugs were not in the field of this work.

Stability studies of monoclonal antibodies carried out in accordance with the recommendations of ICH Guidelines Q5C [2] were selected. These stability studies use at least three complementary methods (study of aggregation [e.g. size exclusion chromatography, turbidimetry], change in chemistry [i.e., peptide mapping] and biological activity [e.g. cytotoxicity on cells, bioassays). Other interesting studies which uses only one or two methods were not selected [3,4].

For some drugs, interesting results were not selected due to various reasons. The stability of bendamustine was studied by Krämer et al. [5] with a 9 hours stability at room temperature and a 5 days in the refrigerator. The results of this study published in 1994 were based on the classical T90% of the initial concentration. However, today, the recommendations of the manufacturer [6] are based on the T95% with a 3.5 hours stability at room temperature and 2 days in the refrigerator. These data were in accordance with the T95% of Krämer et al. We decided to use the recommendation « Follow SPC) ». Moreover, this decision is in accordance with the European guideline for stability studies of anticancer drugs [7].

For vincristine, the extended stability in polyolefine bags was also demonstrated in polypropylene syringes [8] but the information has not been selected because of the recommendations of the World Health Organisation [9] who recommend to prepare the vinca-alcaloids only in infusion bags to avoid inadvertent intrathecal injections.

Below, we present the new informations and their interests in the daily practice. We have separated the long-term and the short-term stability studies. ''Long-term'' has been arbitrarily defined as a stability of at least 2 weeks.

The updated recommendations are presented in Table 1.

Long-term stability studies

These studies can be divided into five categories.

The stability of monoclonal antibodies

The three studies presented here are the first fully validated stability studies according to the ICH guideline Q5C. Several complementary methods have been used to evaluate the stability of rituximab. Various protein characterization methods were used to determine changes in physicochemical properties of rituximab, including size-exclusion chromatography, dynamic light scattering, turbidimetry, cation-exchange chromatography, second-derivative ultraviolet and infrared spectroscopy, and peptide mapping. Cell culture was used to assess biological stability.

The authors have demonstrated a 6 months stability for the infusions at 1 mg/mL in 0.9% sodium chloride in polyolefine container (Freeflex®) [71]. This long-term stability

Table 1 SFPO and ESOP recommendations for the practical stability of anticancer drugs.
Recommandations SFPO et ESOP pour la stabilité pratique des anticancéreux.

Product	Container	Vehicle	Concentration	Recommendations for storage conditions	References
Alemtuzumab				Follow SPC	
Amifostine				Follow SPC	
Asparaginase	Polypropylene	NaCl 0.9%	80 UI/mL	7 days at 2—8 °C	[3]
Azacitidine	Polypropylene syringes	WFI (4 °C)	25 mg/mL	23 days at −20 °C 5 days at 2—8 °C	[10—12]
Bendamustine				Follow SPC	
Bevacizumab	Polypropylene	NaCl 0.9%	2 to 16 mg/mL	90 days at 4 or 25 °C	[1]
Bleomycin				Follow SPC	
Bortezomib	Glass - polypropylene syringes	NaCl 0.9%	Reconstituted: 1 mg/mL	35 days at 2—8 °C	[13,14]
	Glass	NaCl 0.9%	Reconstituted: 2.5 mg/mL	30 days at 2—8 °C	[15]
Busulfan Never freeze busulfan Incompatible with polycarbonate (dimethylacetamide)	2-piece syringes		Non-diluted solution: 6 mg/mL	28 days at 2—8 °C or at room temperature	[16]
	Polypropylene	NaCl 0.9%	Diluted in administration vehicle: 0.5 mg/mL	19 hours at 2 °C—8 °C Protected from light	[17]
	Glass	NaCl 0.9%	Diluted in administration vehicle: 0.5 mg/mL	48 hours at 2—8 °C	
	Polypropylene or glass	NaCl 0.9%	Diluted in administration vehicle: 0.5 mg/mL	36 hours at 13 °C—15 °C Protected from light	
Caelyx				Follow SPC	
Carboplatin	PVC - polyethylene	Dextrose 5%	Diluted in administration vehicle: 0.70—2.15 mg/mL	84 days at 4 °C or 84 days of which 83 days at 4 °C and 1 day at room temperature Protected from light	[18—20]
	Polyethylene - polypropylene	Dextrose 5%	Diluted in administration vehicle: 3.2 mg/mL	30 days at room temperature protected from light	
Carmustine Never use PVC Should be protected from light	Glass - polyethylene	Dextrose 5%	Diluted in administration vehicle: 0.2 mg/mL	48 hours at 4 °C, 2.5 hours in polyethylene at room temperature Protected from light	[21,22]

Table 1 (*Continued*)

Product	Container	Vehicle	Concentration	Recommendations for storage conditions	References
	Polyethylene	Dextrose 5%	Diluted in administration vehicle: 0.1—0.5 mg/mL	4 hours at 25 °C in the light and 48 hours at 4 °C	
	Polyethylene	Dextrose 5%	Diluted in administration vehicle: 1 mg/mL	4 hours at 25 °C and 24 hours at 4 °C	
Cisplatin	Ethyl vinyl acetate - polyethylene - PVC	NaCl 0.9%	Diluted in administration vehicle: 0.5—0.9 mg/mL 0.1—0.4 mg/mL (PVC)	28 days at room temperature Protected from light	[23—25]
Cladribine	PVC, polyethylene	NaCl 0.9%	Diluted in administration vehicle: 0.016 mg/mL	30 days at 4 °C and at 18 °C	[26]
Clofarabine	Polyolefine	Dextrose 5% or NaCl 0.9%	0.2—0.6 mg/mL	28 days at room temperature without protection from light or at 4 °C protected from light	[27]
cyclophosphamide	Verre	NaCl0.9%	0.4 mg/mL	14 days at 2—8 °C protected from light	[28]
	PVC	Dextrose 5% or NaCl 0.9%	Diluted in administration vehicle: 1 mg/mL	7 days at 4 °C and at room temperature Protected from light	[29,30]
Cytarabine	PVC	NaCl 0.9%	Diluted in administration vehicle: 0.018 mg/mL	29 days at 23 °C or 2 °C	[31]
	EVA	Dextrose 5% or NaCl 0.9%	Diluted in administration vehicle: 1.25 and 25 mg/mL	28 days at 25 °C or 4 °C protected from light	[32]
Dacarbazine Toxic products may form if the solution is not protected from light Must be administered protected from light (bag + tubing)	Amber glass	Dextrose 5%	Reconstituted: 11 mg/mL	7 days at 4 °C and 4 days at room temperature Protected from light	[33]
	PVC	Dextrose 5%	Diluted in administration vehicle: 1.5 mg/mL	7 days at 4 °C and 3 days at room temperature protected from light	
	PVC - polyethylene	NaCl 0.9%	Diluted in administration vehicle: 0.640 mg/mL	2 days at room temperature in the light and at 4 °C	

Table 1 (*Continued*)

Product	Container	Vehicle	Concentration	Recommendations for storage conditions	References
Dactinomycin	PVC	Dextrose 5%	Diluted in administration vehicle: 0.01 mg/mL	24 hours in the light and at room temperature	[34]
Daunorubicin At concentrations > 0.5 mg/mL daunorubicin is not photosensitive for at least 7 days	PVC Polypropylene	Dextrose 5% or NaCl 0.9% WFI	Diluted in administration vehicle: 0.1 mg/mL Diluted in administration vehicle: 2 mg/mL	43 days at −20 °C, 4 °C and 25 °C 43 days at 4 °C	[35,36]
Daunoxome				Follow SPC	
Dexrazoxane	PVC Polyethylene Polyethylene	Ringer Lactate Ringer Lactate Ringer Lactate	Diluted in administration vehicle: 4 and 8 mg/mL Diluted in administration vehicle: 8 mg/mL Diluted in administration vehicle: 4 mg/mL	8 hours at 25 °C in the light 8 hours at 25 °C in the light 4 hours at 25 °C in the light	[37]
Docetaxel (two vials) (after reconstitution: 10 mg/mL) Avoid PVC containers	Glass Polypropylene - polyethylene	Special solvent NaCl 0.9% or dextrose 5%	Reconstituted: 10 mg/mL Diluted in administration vehicle: 0.3—0.9 mg/mL Diluted in administration vehicle: 0.3—0.9 mg/mL	28 days at 2 °C—8 °C and at 25 °C 28 days at 25 °C Protected from light 56 days at 25 °C, 2—8 °C protected from light	[38] [38,39]
Docetaxel (one vial) (solution at 20 mg/mL) Avoid PVC containers	Polyolefine	NaCl 0.9% or dextrose 5%	Diluted in administration vehicle: 0.24 > 1 mg/mL	28 days at 20 °C, 5 °C Protected from light	[40]
Doxorubicin At concentrations > 0.5 mg/mL Doxorubicin is not photosensitive for at least 7 days	Polypropylene PVC	NaCl 0.9% Dextrose 5% or NaCl 0.9%	Diluted in administration vehicle: 1—2 mg/mL Diluted in administration vehicle: 0.1 mg/mL	124 days at 4 °C and 23 °C 24 days at 25 °C and 43 days at 4 °C or −20 °C	[41] [41,42]
Epirubicin At concentrations > 0.5 mg/mL epirubicin is not photosensitive for at least 7 days	Polypropylene PVC	NaCl 0.9% Dextrose 5% or NaCl 0.9%	Diluted in administration vehicle: 1—2 mg/mL Diluted in administration vehicle: 0.1 mg/mL	150 days at 23 °C and at 4 °C 20 days at 25 °C and 43 days at 4 °C or −20 °C	[43] [41,42]
Eribuline mesylate	Polypropylene	None	440 μg/mL	14 days at 4 °C or 20 °C with or without protected from light	[44]

Table 1 (*Continued*)

Product	Container	Vehicle	Concentration	Recommendations for storage conditions	References
	Polyolefine	NaCl 0.9%	Diluted in administration vehicle: 15.4 and 43.3 μg/mL	14 days at 4 °C or 20 °C with or without protected from light	
Etoposide	Polypropylene	NaCl 0.9%	Diluted in administration vehicle: 0.2 mg/mL	96 hours at < 25 °C in the light	[45]
	Polypropylene	NaCl 0.9%	Diluted in administration vehicle: 0.4 mg/mL	24 hours at < 25 °C in the light	
Etoposide phosphate	Glass	WFI	Reconstituted: 10 and 20 mg/mL	31 days at 23 °C and 4 °C	[46]
	PVC	NaCl 0.9% or dextrose 5%	0.1—10 mg/mL	31 days at 23 °C and at 4 °C	
Fludarabine		NaCl 0.9%	Diluted in administration vehicle: 0.04 to 1 mg/mL	21 days at 25 °C or at 8 °C protected from light	[47]
Fluorouracil	Glass or PVC	NaCl 0.9% or dextrose 5%	Diluted in administration vehicle: 1.5 mg/mL	8 weeks at room temperature in the light	[48]
Folinate calcium	Glass	Dextrose 5% or NaCl 0.9%	Reconstituted: 20 mg/mL	4 days at 4 °C or 25 °C Protected from light	[49]
	Glass or PVC	Dextrose 5% or NaCl 0.9%	Diluted in administration vehicle: 0.1—0.5 mg/mL	24 hours at 4 °C or 25 °C (adsorption on PVC at low concentrations)	
	Glass or PVC	Dextrose 5% or NaCl 0.9%	Diluted in administration vehicle: 1—1.5 mg/mL	4 days at 4 °C or 25 °C in the light	
Folinate sodium	Polyethylene	Dextrose 5%	Diluted in administration vehicle: 3.2 mg/mL	90 days at −20 °C or 30 days at 4 °C, protected from light	[50]
Fotemustine Administer protected from light	PVC	Dextrose 5%	Diluted in administration vehicle: 0.2—2 mg/mL	2 days at 4 °C and 8 hours at room temperature, protected from light	[51]
Gemcitabine	Polypropylene syringes	NaCl 0.9%	Reconstituted: 38 mg/mL	35 days at room temperature	[52]
	PVC	NaCl 0.9% or Dextrose 5%	Diluted in administration vehicle: 1—10 mg/mL	35 days at 4 °C and 7 days at 23 °C—32 °C	
Idarubicin	Polypropylene	Dextrose 5% or NaCl 0.9%	Diluted in administration vehicle: 0.1 mg/mL	28 days at ≤ 25 °C Protected from light	[53]
Ifosfamide	PVC	Dextrose 5% or NaCl 0.9%	Diluted in administration vehicle: 30 mg/mL	30 days at 4 °C Protected from light	[54]

Table 1 (*Continued*)

Product	Container	Vehicle	Concentration	Recommendations for storage conditions	References
	PVC	Dextrose 5% or NaCl 0.9%	Diluted in administration vehicle: 0.6—40 mg/mL	4 days at 4 °C or room temperature Protected from light	
Interleukin 2				Follow SPC	
Irinotecan	PVC	Dextrose 5% or NaCl 0.9%	Diluted in administration vehicle: 0.4 to 2.8 mg/mL	28 days at room temperature or 2—8 °C Protected from light	[55]
Levofolinate calcium	Polyethylene	Dextrose 5%	Diluted in administration vehicle: 1.6 mg/mL	95 days at −20 °C and 30 days at 2—8 °C	[56]
Melphalan Dextrose 5% must not be used The degradation of melphalan increases with the temperature	PVC	NaCl 3%	Diluted in administration vehicle: 0.2 mg/mL	48 hours at 4 °C and 3 hours at 26 °C in the light	[57]
	PVC, polyethylene	NaCl 0.9%	Diluted in administration vehicle: 0.06 mg/mL	24 hours at 4 °C and 1 hour at room temperature Protected from light	[58]
Methotrexate	Polypropylene syringes	NaCl 0.9%	Diluted in administration vehicle: 2.5 mg/mL	7 days at room temperature and at 4 °C Protected from light	[59]
	PVC	NaCl 0.9% or dextrose 5%	Diluted in administration vehicle: 0.225—24 mg/mL	30 days at 4 °C Protected from light	[60]
Mitomycin				Follow SPC	
Mitoxantrone	Glass bottle	Ready-to-use solution	2 mg/mL	42 days at 4 °C and at 23 °C	[61]
	PVC	NaCl 0.9% or Dextrose 5%	Diluted in administration vehicle: 0.04—0.4 mg/mL	7 days at 4 °C and at 23 °C Protected from light	[62]
Myocet				Follow SPC	
Nelarabine	Ethylene vinyl acetate	None	5 mg/mL	28 days at 2—8 °C protected from light or at 25 °C in presence of light	[63]

Table 1 (*Continued*)

Product	Container	Vehicle	Concentration	Recommendations for storage conditions	References
Oxaliplatin	Polyolefin bags	Dextrose 5%	Diluted in administration vehicle: 0.25 mg/mL	90 days at 4 °C protected from light or at room temperature with or without protection from light	[64]
	Polyolefin bags	Dextrose 5%	Diluted in administration vehicle: 0.7 mg/mL	30 days at room temperature protected from light	[65]
Paclitaxel Exclude PVC containing DEHP Is less stable at increasing concentration or temperature due to increased risk of precipitation	Polypropylene	NaCl 0.9% or dextrose 5%	Diluted in administration vehicle: 0.3—1.2 mg/mL	4 days at 25 °C and 12 days at 5 °C Protected from light	[66,67]
	Polyethylene	NaCl 0.9% or dextrose 5%	Diluted in administration vehicle: 0.3 mg/mL	13 days at 2 °C—8 °C Protected from light	
	Polyethylene	NaCl 0.9% or dextrose 5%	Diluted in administration vehicle: 1.2 mg/mL	9 days at 2 °C—8 °C Protected from light	
Pemetrexed If stored at 4 °C (microparticles might form), a 0.22 μm in-line filter has to be used	Polypropylene syringes	NaCl 0.9% or dextrose 5%	Diluted in administration vehicle: 25 mg/mL	2 days at room temperature and 31 days at 4 °C Protected from light	[68,69]
	PVC bags	NaCl 0.9%	Diluted in administration vehicle: 5 mg/mL	28 days at 4 °C Protected from light	
Pentostatin	Glass PVC	NaCl 0.9% NaCl 0.9%	Reconstituted: 2 mg/mL Diluted in administration vehicle: 0.002—0.02 mg/mL	3 days 48 hours at 23 °C	[70]
Rituximab	Polyolefine	NaCl 0.9%	1 mg/mL	180 days at 4 °C	[71]
Streptozocin				Follow SPC	
Temsirolimus	Polypropylene	NaCl 0.9%	0.1 mg/mL	3 days at 20 °C protected from light 4 days at 2—8 °C	[72]
Thiotepa	PVC, polyolefin	Dextrose 5%	Diluted in administration vehicle: 5 mg/mL	3 days at 4 °C and at room temperature in the light	[73,74]

Table 1 (*Continued*)

Product	Container	Vehicle	Concentration	Recommendations for storage conditions	References
	PVC	NaCl 0.9%	Diluted in administration vehicle: 0.5—3 mg/mL	2 days at 8 °C and 1 day at room temperature in the light	
Topotecan	PVC	NaCl 0.9% or dextrose 5%	Diluted in administration vehicle: 0.025, 0.05 mg/mL	28 days at 4 °C and at room temperature Protected from light	[75]
	Elastomere	NaCl 0.9% or dextrose 5%	Diluted in administration vehicle: 0.01 and 0.05 mg/mL	21 days at 25 °C not Protected from light	
	PVC	NaCl 0.9%	Diluted in administration vehicle: 0.01 mg/mL	7 days at room temperature in the light	
Trastuzumab	Polypropylene	NaCl 0.9%	Diluted in administration vehicle: 0.8 mg/mL	180 days at 4 °C	[76]
Vinblastine	Glass	WFI	Reconstituted: 1 mg/mL	21 days at 4 °C Protected from light	[77,78]
	Polypropylene	NaCl 0.9% or dextrose 5%	Diluted in administration vehicle: 0.02 mg/mL	21 days at 4 °C and at 25 °C Protected from light	
	PVC	NaCl 0.9% or dextrose 5%	Diluted in administration vehicle: 0.1 mg/mL	7 days at 4 °C Protected from light	
Vincristine	Polypropylene	NaCl 0.9% or dextrose 5%	Diluted in administration vehicle: 0.02 mg/mL	21 days at 4 °C and at 25 °C Protected from light	[77,79]
	PVC polypropylene	NaCl 0.9%	Diluted in administration vehicle: 0.01 to 0.15 mg/mL	7 days at 4 °C Protected from light	
	Polyolefin	NaCl 0.9%	Diluted in administration vehicle: 0.05 mg/mL	84 days at 2—8 °C protected from light or at 25 °C	[8]
Vindesine	Glass	WFI	Reconstituted: 1 mg/mL	21 days at 4 °C Protected from light	[77]
	Polypropylene	NaCl 0.9% or dextrose 5%	Diluted in administration vehicle: 0.02 mg/mL	21 days at 4 °C and at 25 °C Protected from light	
Vinorelbine	PVC, polyethylene	NaCl 0.9%	Diluted in administration vehicle: 0.385 mg/mL	7 days at 23 °C	[78,80,81]
	PVC	Dextrose 5%	Diluted in administration vehicle: 0.5 mg/mL	7 days at 4 °C	

study allows the standardization of the dose by different manner. The large-scale production of doses at 600, 700, 800 and 900 mg has been carried out at the pharmacy of the University hospital of Créteil in France.

Other approaches using these results have been developed in other hospitals like the preparation in advance for a specified patient. The organization is in accordance with the Dose Banding Concept with a maximum deviance of 5% between the dose administered and the dose calculated according to the body surface area (BSA). In the university hospital of Nancy, France doses of rituximab are standardized between 570 and 870 mg by band of 60 mg. For doses between 570 and 630 mg, a rounded dose of 600 mg is prepared; for doses between 630 and 690 mg, we prepare 660 mg, etc [82].

If the treatment is cancelled or postponed, the infusion is re-used for another patient and another label is put on the infusion bag according to a specialized procedure. This possibility has been written in the standard of ISOPP in chapter 20 where there are recommendations for the re-use of drugs [83].

As rituximab is always almost used for outpatient, it is very important to have an immediate availability of the preparation after the prescription. This preparation in advance allow other advantages, it decrease the stress of the pharmaceutical team who can prepared in advance outside the hours of the main activity in the afternoon, it decrease the stress of the nursing staff who do not wait for the treatment and it allow also important cost savings.

A similar organization has be performed for bevacizumab infusions with 3 months stability for the solution diluted in 0.9% sodium chloride in polyolefine bags[1] and for trastuzumab with 6 months stability for the 0.8 mg/mL solution stored at 4 °C [76].

Stability studies of classical molecules to allow the Dose Banding concept

Long-term stability have been demonstrated for cisplatine docetaxel, fludarabine, oxaliplatine and vincristine. For azacitidine, the long-term stability has been demonstrated for the frozen suspension.

Vincristine is mainly administered as a 2 mg infusion and therefore is an easy drug for the standardization. A 84 days stability has been demonstrated in polyolefine containers allowing the batch scale production in advance.

For the other drugs, extended stability have been demonstrated (28 days for cisplatine [23], 28 days for the new formulation of docetaxel (ready to use solution at 20 mg/mL) and 56 days for the formulation at 10 mg/mL [39,40], 21 days for fludarabine phosphate [47], and 90 days for oxaliplatine [64]. This allows the standardization of the doses and the batch production or the preparation in advance for one patient and the re-use of the drug if the administration is cancelled or postponed.

Azacitidine has been approved for the treatment of myelodysplasic syndromes and acute myeloid leukemia, this drug is administered as a suspension at 25 mg/mL by subcutaneous injections daily during one week.

Azacitidine is a very unstable drug with a stability of 45 minutes at room temperature and 8 hours at 2—8 °C. This stability has been further enhanced by the manufacturer with a 22 hours stability if the powder is reconstituted with cold water for injection [84]. The 22 hours stability does not allow the preparation in advance especially for the weekend.

This drug was used 25 years ago and administered as intravenous infusions at diluted concentrations of 0.2 mg/mL. Two stability studies have demonstrated that the solutions are very unstable but no stability study of the suspension had been published [85,86].

In the stability study selected [10], the suspension at 25 mg/mL was stable for 8 days at −20 °C allowing the production in advance especially for the weekend and important cost savings (one vial cost 340 euros). In this study, the vials were reconstituted with ice-cold water for injection to optimize the T0 concentration. The reconstitution with water for injection at room temperature should be avoided because of an immediate 4% drop in the concentration after reconstitution.

The thawing of the frozen suspensions were performed at room temperature for 45 minutes and then the syringe were stable for 8 hours at 4 °C.

A more recent study submitted for publication was presented during the last congress of the French society of Oncology Pharmacists[2] and during the last ECCO congress in Stockholm, the presentation is available on the Stabilis website [11]. The study demonstrated a 5 days stability at 4 °C after reconstitution with ice-cold water for injection.

A Canadian publication recently extends the stability of the frozen suspension at 23 days allowing the possibility of Dose Banding (syringes at 55, 60, 65, 70, 75 mg) [12].

Stability studies of adjuvant therapy

The stability of levofolinate calcium, folinate sodium has been demonstrated after freezing and microwave thawing to allow the batch production in Centralized Intravenous Additive Service (CIVAS).

Freezing and microwave thawing is mainly developed for antibiotic therapy and allow the delivery of ready-to-use infusions to the wards. The organization has been developed in North America but also in Europe [87]. It can also be used for adjuvant therapy.

In the study selected, levofolinate calcium and folinate sodium infusions were stable for 90 days at −20 °C and then 30 days at 2 to 8 °C [50,56].

[1] Morand K, Paul M, Lahlou A, Blanchet B, Astier A. Stabilité de solutions diluées de bévacizumab en fonction de la température. Poster presented at the SFPO Congress Mandelieu, France 2009 (Submitted to publication), available on Stabilis.(www.stabilis.org).

[2] Vieillard V, Appudurai O, Voytenko S, Astier A, Paul M. Stabilité physico-chimique de la suspension d'azacitidine (25 mg/mL) conservée à 4 °C. Poster presented SFPO Congress Mandelieu, France 2011 (submitted to publication), available on Stabilis.(www.stabilis.org).

Stability studies of rarely used molecules

(clofarabine, eribuline mesylate and nelarabine) to allow the production in advance or to keep the infusion if the administration is canceled or postponed.

Clofarabine is a halogenated-adenosine analogue approved for the treatment of relapsed or refractory hematologic malignancies (acute lymphoblastic leukemia [ALL] or acute myeloid leukemia [AML]).

Ready-to-use clofarabine infusions (0.2 and 0.6 mg/mL) in polyolefine bags in 0.9% NaCl and 5% glucose are physico-chemical stable over at least 28 days when refrigerated or stored at room temperature [27].

Nelarabine, a new purine nucleoside analogue, was approved in 2007 by the EMA for the treatment of T-cell acute lymphoblastic leukaemia and T-cell lymphoblastic lymphoma.

The commercially available solution for infusion is not diluted before administration. The appropriate volume of nelarabine solution for infusion is transferred into ethylene vinyl acetate (EVA) or polyvinylchloride (PVC) infusion in paediatric patients [63].

In the stability study selected, ready-to-use nelarabine infusion solutions in EVA infusion bags were physico-chemically stable for at least four weeks, either refrigerated or at ambient temperature, and with or without protection from light.

Eribuline mesylate received approval by the European Medicines Agency in March 2011 for the treatment of advanced breast cancer patients who have received at least two prior chemotherapeutic regimens for late-stage disease, including both anthracycline- and taxane-based chemotherapies.

Each vial contains 0.88 mg of eribuline mesylate as a 440 μg/mL solution in ethanol-water (5:95, v/v). This drug is administered undiluted or diluted in 0.9% sodium chloride solution.

In the selected study, ready-to-use solutions at 440 μg/mL in polypropylene syringes and dilutions in 0.9% sodium chloride in polyolefine containers at 15.4 and 343.3 μg/mL were physically compatible and chemically stable for at least 14 days at 4 °C in the refrigerator and at 20 °C with or without any protection against light [44].

The three drugs are very expensive and these long-term stability studies allow the re-use of the preparation if the administration is canceled or postponed.

Short-term stability studies

L-Asparaginase (Kidrolase®) is an enzyme from *Escherichia coli* used for the treatment of lymphocytic leukemia. Only one stability study was carried out by using the enzymatic activity as biological criteria to evaluate the stability [88]. The authors had studied dilutions in serum saline and ringer lactate in polyolefine and polyethylene bags. The enzymatic activity proved to be stable for 7 days after storage at 8 °C with only a 8% drop in activity.

The presented work is the first study evaluating the stability by using several physico-chemical methods according to the ICH Q5C recommendations[3]. Size exclusion chromatography (SEC), dynamic light scattering (DLS) describing submicronic populations and corresponding mean diameter, turbidity at 350 nm, thermal aggregation curves and determination of L-Aspa concentration by UV at 280 nm (chemical stability) have been used to evaluate the stability. The enzymatic activity was also investigated. The authors have demonstrated a 7 days stability at 4 °C for a normal saline solution at 80 UI/mL in Freeflex® bags. This extended stability allow the preparation in advance especially for the weekend, the drug being prescribed every 2 days in various protocols.

Temsirolimus received approval by the European Medicines Agency (EMA) in November 2007 for the treatment of advanced renal cell carcinoma and in September 2011 for the treatment of adult patients with relapsed or refractory mantle cell lymphoma.

Temsirolimus is administered as a solution to be given by intravenous infusion over 30 to 60 minutes. The finished product, Torisel®, is a two-vial system consisting of a concentrate solution containing 25 mg/mL temsirolimus (in one vial) and a specifically formulated diluent (in another vial) composed of polysorbate 80, polyethylene glycol 400, dehydrated alcohol and nitrogen.

Light is the most important factor influencing stability of the drug; sunlight can have a dramatic effect on the stability of diluted solutions in polypropylene containers. The second factor that influences the rate of temsirolimus degradation is the temperature.

Ready-to-use temsirolimus infusion solutions could be stored, protected from light, 4 days at 4 °C and 3 days at 20 °C. The degradation rate under artificial light is sufficiently low to authorize the absence of opaque infusion sets. However, the exposition to sunlight must be absolutely avoided [72].

Conclusion

These recommendations have to be taken into consideration only if the preparation is carried out according to the Good Manufacturing Practices in classified rooms. Biological Safety Cabinet or isolators have to be used for the production and the preparation process has to be validated to prove the sterility of the syringes or infusions.

The use of these stability data can have a great impact for the patient (waiting time reduced or eliminated), for the pharmaceutical (workload facilitated), for the nursing staff (better availability of infusions) and for the economical aspects (saving of vials).

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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