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Let us close the gap

Klaus Meier
Editor-in-Chief
EJOP

Five years ago, the Treaty of Lisbon came into force, which formed the constitutional basis of the European Union. In May 2014, the new European Parliament, comprising 27 neighbour countries, was elected under the framework of the new EU constitution, creating a unified nation. In Article 2 (1a) the European Union nations declared:

> *'The Union is founded on the values of respect for human dignity, freedom, democracy, equality, the rule of law and respect for human rights including the rights of persons belonging to minorities. These values are common to the Member States in a society together, which is characterized by pluralism, non-discrimination, tolerance, justice, solidarity and equality between women and men prevail.'* Available from: www.eurotreaties.com/lisbontext.pdf

Who would have thought that these goals in the Treaty of Lisbon would demand the real support from us especially in connection with the conflict of interest in Eastern Europe as is happening today.

At the same time, the elections to the European Parliament have shown that uncertainty still exists, and that it is necessary for people to co-operate more closely.

Racism, fear of loss, or even exaggerated nationalism can be found as a catch-all for all those who are not aware of the dangers of their existence through negation of common goals.

The mission of the European Society of Oncology Pharmacy (ESOP), and therefore my role as President, is not to formulate general policy objectives. Rather, we must use our experience over the past 15 years in Europe to foster cross-border co-operation to ensure that benefits are created for sick people.

We have made it clear that our fellow human beings, wherever they live in Europe, have a right to equal treatment for their diseases in addition to economic equality. We have mapped out common goals on the standard of pharmaceutical services to physicians, nurses and patients, and ESOP's fifth edition of QuapoS guidelines for nurses, shortly to be released, is an example of this.

Similarly, over the past eight years, we have implemented a programme of mutual training and exchange of practical and theoretical experience, and have run European Masterclasses and workshops in Luxembourg.

Now, on the eve of the European Conference of Oncology Pharmacy, we must take this opportunity to demonstrate our relationships to all those who are willing and able partner and collaborate in Europe.

It is our responsibility to drive forward our goals and fulfill the pledges that we have made to all our European members and those who feel like we do. By doing so, we feel that we are leading by example and hope to inspire colleagues to feel and live like our European fathers have foretold.

Heal all wounds and save human life. Fight against cancer and not against humans. Let us build a nation that is a good partner to all its neighbours. Let us learn our mission and become an important part of all healthcare teams. Let us do our work.

EJOP – Call for papers

The main objectives of the *European Journal of Oncology Pharmacy* (EJOP) are providing information on current developments in oncology treatment, sharing practice related experiences as well as offering an educational platform via conference/seminar reports to practising oncology pharmacists and pharmacy technicians. The editorial content covers scientific, clinical, therapeutic, economic and social aspects. Prospective authors are welcome and invited to share their original knowledge and professional insight by submitting papers concerning drug developments, safety practices in handling cytotoxics and breakthroughs in oncology treatment along with practice guidelines and educational topics which fall within the scope of oncology pharmacy practice. Manuscripts must be submitted in English, the journal offers English support to the manuscript content. The EJOP 'Guidance for Authors' can be found on the website (www.ejop.eu), where the journal is freely available in PDF format. You are encouraged to discuss your ideas for manuscripts with us at editorial@ejop.eu.

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

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

Introduction

The recommended storage conditions for anticancer drugs are the result of deliberations by the *Société Française de Pharmacie Oncologique* (French Society of Oncology Pharmacy, SFPO) stability group. The first edition of the data was published in 2008 by the *Centre National Hospitalier d'Information sur le Médicament*. The stability group included Philippe Arnaud, Alain Astier, Agnès Bellanger, Brigitte Bonan, Dominique Breilh, Sylvie Burnel , Mikaël Daouphars, Anne Laure Ferrio, Laurent Havard, Alix Helvig, Marie Caroline Husson, Frédéric Pinguet, Nicole Poisson, Bernard Sarrut, Jean Vigneron. These recommendations were adopted as the European standard by European Society of Oncology Pharmacy in 2010, and published in the *European Journal of Oncology Pharmacy* [1].

A new group, involving members of SFPO and European hospital pharmacists, updated this work in 2012. This new group involved 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.

The update included the following new drugs: asparaginase, azacitidine, bevacizumab, clofarabine, eribuline mesylate, folinate sodium, levofolinate calcium, nelarabine, rituximab, temsirolimus. Information on some drugs were updated (cisplatine, docetaxel, fludarabine, oxaliplatine, vincristine), and three drugs (chlormethine, mitoguazone and pirarubicine) no longer available on the market were removed.

Selection criteria for articles

The Stabilis database was used to select new information. The cut-off date for included articles was 2008. A checklist for physical and chemical stability was used to select relevant articles, and these were only included if they added new information to daily practice, e.g. extended stability for advance preparation. We decided to include information presented in posters if the stability study conformed to our criteria and had been submitted for publication. Stability data of simple solutions (one drug in one container) were selected, however, the stability of mixtures or of non-injectable drugs was not included.

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

For some drugs, interesting results were not selected for various reasons. The stability of bendamustine was studied by Krämer et al. [5], with nine hours stability at room temperature and five days in the refrigerator. The results of this study published in 1994 were based on the classical T90% of the initial concentration. Today, however, the recommendations of the manufacturer [6] are based on the T95%, with three and half hour stability at room temperature and two days in the refrigerator. These data are in accordance with the T95% of Krämer et al. [5], we decided to use the recommendation 'Follow summary of product characteristics'. Moreover, this decision is in accordance with the European guideline for stability studies of anticancer drugs [7].

For vincristine, extended stability in polyolefin bags was also demonstrated in polypropylene syringes [8], but this information was not selected because the World Health Organization recommends preparation of vinca-alcaloids only in infusion bags to avoid inadvertent intrathecal injections [9].

Below, we present the new information obtained and highlight areas of interest for daily practice. We have separated these data into long-term and short-term stability studies. 'Long-term' has been arbitrarily defined as a stability of at least two weeks.

Long-term stability studies

Long-term stability studies can be divided into four categories. These are described below.

The stability of monoclonal antibodies

The three studies presented here are the first fully validated stability studies according to the ICH guideline Q5C.

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Several complementary methods have been used to evaluate the stability of rituximab (MabThera). 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 investigators demonstrated six months stability for the infusions at 1 mg/mL in 0.9% sodium chloride in polyolefin container (Freeflex) [10]. This long-term stability study allowed dose standardization using a different method. 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.

Approaches using these results have also been developed in other hospitals, e.g. advance preparation for a specified patient. This is in accordance with the dose-banding concept, which has a maximum deviance of 5% between the dose administered and the dose calculated according to the body surface area. In the University Hospital of Nancy, France, doses of rituximab are standardized between 570 mg and 870 mg by band of 60 mg. For doses between 570 mg and 630 mg, a rounded dose of 600 mg is prepared; for doses between 630 mg and 690 mg, for example, we prepare 660 mg [11].

If the treatment is cancelled or postponed, the infusion is reused for another patient, and a new label is placed on the infusion bag according to a specialized procedure. This scenario is outlined in the ISOPP Standards of Practice, chapter 20, which makes recommendations for the reuse of drugs [12].

Rituximab is almost always prescribed to outpatients. It is, therefore, important that the preparation is immediately available after clinic. Preparing this drug in advance offers other advantages: it reduces stress among the pharmaceutical team as they can prepare the drug in advance in less busy periods, and it reduces the stress of nursing staff who do not have to wait for the treatment. It also enables important cost savings to be made.

A similar process is carried out for bevacizumab infusions, with three month stability for the solution diluted in 0.9% sodium chloride in polyolefin bags [13] and, for trastuzumab, with six months stability for the 0.8 mg/mL solution stored at 4°C [14].

Stability studies of classical molecules to allow the dose-banding concept

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

Vincristine is mainly administered as a 2 mg infusion, and is therefore an easy drug to standardize. An 84-day stability has been demonstrated in polyolefin containers, allowing advance batch-scale production.

For the other drugs, extended stability has been demonstrated: 28 days for cisplatine [15], 28 days for the new formulation of docetaxel (ready to use solution at 20 mg/mL), 56 days for the formulation at 10 mg/mL [16, 17], 21 days for fludarabine phosphate [18], and 90 days for oxaliplatine [19]. This enables standardization of doses and batch production, or advance preparation for one patient and the reuse of the drug if the administration is cancelled or postponed.

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

Azacitidine is an unstable drug, with a stability of 45 minutes at room temperature and eight hours at 2–8°C. This stability has been further enhanced by the manufacturer with a 22-hour stability if the powder is reconstituted with cold water for injection [20]. The 22-hour stability does not allow advance preparation, especially for weekends.

This drug was used 25 years ago, and administered as intravenous infusions at diluted concentrations of 0.2 mg/mL. Two stability studies [21, 22] have demonstrated that the solutions are unstable, but no stability study of the suspension has been published.

In the stability study selected [23], the suspension at 25 mg/mL was stable for eight days at -20°C, allowing advance production, especially for weekends, and important cost savings to be made (one vial cost Euros 340). In this study, the vials were reconstituted with ice-cold water for injection to optimize the T0 concentration. 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 was carried out at room temperature for 45 minutes, and the contents stabilized in a syringe for eight hours at 4°C.

A more recent study (unpublished data) was presented during the last congress of the French Society of Oncology Pharmacy [24], and during the European CanCer Organisation (ECCO) 2011 Congress in Stockholm, Sweden. The presentation is available on the Stabilis website [25]. The study demonstrated five days stability at 4°C after reconstitution with ice-cold water for injection.

A Canadian publication recently extended the stability of the frozen suspension at 23 days, allowing the possibility of dose banding (syringes at 55, 60, 65, 70, 75 mg) [26].

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Stability studies of adjuvant therapy

The stability of calcium levofolinate and sodium folinate has been demonstrated after freezing and microwave thawing to allow batch production using the centralized intravenous additive service.

Freezing and microwave thawing is mainly developed for antibiotic treatments, and allows the delivery of ready-to-use infusions to the wards. The organization has been developed in the US and in Europe [27]. It can also be used for adjuvant therapy. In the study selected, calcium levofolinate and sodium folinate infusions were stable for 90 days at –20°C and then 30 days at 2–8°C [28, 29].

Stability studies of rarely used molecules

Clofarabine, nelarabine and eribulin mesylate can be prepared in advance or the infusion stored if administration is cancelled or postponed.

Clofarabine

Clofarabine is a halogenated-adenosine analogue approved for the treatment of relapsed or refractory haematologic malignancies—acute lymphoblastic leukaemia or acute myeloid leukaemia. Ready-to-use clofarabine infusions (0.2 and 0.6 mg/mL) in polyolefin bags in 0.9% NaCl and 5% glucose are physicochemical stable over at least 28 days when refrigerated or stored at room temperature [30].

Nelarabine

Nelarabine (Atriance) is a purine nucleoside analogue, and was approved in 2007 by the European Medicines Agency (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 or polyvinylchloride infusion in children [31].

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

Eribulin mesylate

Eribulin mesylate (Halaven) received approval by EMA in March 2011 for the treatment of women with advanced breast cancer 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 polyolefin 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 [32].

The three drugs are expensive, and these long-term stability studies allow the reuse of the preparation if the administration is cancelled or postponed.

Short-term stability studies

L-asparaginase (Kidrolase) is an enzyme from *Escherichia coli* used for the treatment of lymphocytic leukaemia. Only one stability study was carried out by using the enzymatic activity as biological criteria to evaluate the stability [33]. The investigators had studied dilutions in serum saline and ringer lactate in polyolefin and polyethylene bags. The enzymatic activity proved to be stable for seven days after storage at 8°C with only an 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 [34]. Size exclusion chromatography, dynamic light scattering describing sub-micronic populations and corresponding mean diameter, turbidity at 350 nm, thermal aggregation curves and determination of L-asparaginase concentration by UV at 280 nm (chemical stability) have been used to evaluate the stability. The enzymatic activity was also investigated. The investigators demonstrated seven days stability at 4°C for a normal saline solution at 80 UI/mL in Freeflex bags. This extended stability allows advance preparation, especially for weekends, the drug being prescribed every two days in various protocols.

Temsirolimus (Torisel) received approval by EMA in November 2007 for the treatment of advanced renal cell carcinoma, and in September 2011 for the treatment of adults with relapsed or refractory mantle cell lymphoma.

Temsirolimus is administered as a solution to be given by intravenous infusion over 30–60 minutes. The finished product, Torisel, is a two-vial system consisting of a concentrated 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, four days at 4°C and three days at 20°C. The degradation rate under artificial light is sufficiently low to authorize the absence of opaque infusion sets. Exposure to sunlight, however, must be absolutely avoided [35].

Conclusion

These recommendations have to be considered only if the preparation is carried out in accordance with good manufacturing

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Table 1: SFPO and ESOP recommendations for the practical stability of anticancer drugs

Product	Container	Vehicle	Concentration	Recommended storage conditions	References
ALEMTUZUMAB				Follow SmPC	
AMIFOSTINE				Follow SmPC	
ASPARAGINASE	Polypropylene	NaCl 0.9%	80 UI/mL	7 days at 2–8°C	34
AZACITIDINE	Polypropylene syringes	WFI (4°C)	25 mg/mL	23 days at –20°C 5 days at 2–8°C	23, 24, 26
BENDAMUSTINE				Follow SmPC	
BEVACIZUMAB	Polypropylene	NaCl 0.9%	2 to 16 mg/mL	90 days at 4 or 25°C	13
BLEOMYCIN				Follow SmPC	
BORTEZOMIB	Glass-polypropylene syringes	NaCl 0.9%	Reconstituted: 1 mg/mL	35 days at 2–8°C	36, 37
	Glass	NaCl 0.9%	Reconstituted: 2.5 mg/mL	30 days at 2–8°C	38
BUSULFAN - Never freeze busulfan - Incompatible with polycarbonate (Dimethylacetamide)	Two-piece syringes		Non-diluted solution: 6 mg/mL	28 days at 2–8°C or at room temperature	39
	Polypropylene	NaCl 0.9%	0.5 mg/mL	19 hours at 2–8°C protected from light	40
	Glass	NaCl 0.9%	0.5 mg/mL	48 hours at 2–8°C	
	Polypropylene or glass	NaCl 0.9%	0.5 mg/mL	36 hours at 13–15°C protected from light	
CAELYX				Follow SmPC	
CARBOPLATIN	PVC – polyethylene	Dextrose 5%	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	41, 42, 43
	Polyethylene – polypropylene	Dextrose 5%	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%	0.2 mg/mL	48 hours at 4°C, 2.5 hours in polyethylene at room temperature protected from light	44, 45
	Polyethylene	Dextrose 5%	0.1– 0.5 mg/mL	4 hours at 25°C in the light and 48 hours at 4°C	
	Polyethylene	Dextrose 5%	1 mg/mL	4 hours at 25°C and 24 hours at 4°C	
CISPLATIN	Ethyl vinyl acetate – polyethylene – PVC	NaCl 0.9%	0.5–0.9 mg/mL 0.1–0.4 mg/mL (PVC)	28 days at room temperature protected from light	46, 47, 15
CLADRIBINE	PVC, polyethylene	NaCl 0.9%	0.016 mg/mL	30 days at 4°C and at 18°C	48

(*Continued*)

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Table 1: SFPO and ESOP recommendations for the practical stability of anticancer drugs (*Continued*)

CLOFARABINE	Polyolefin	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	30
CYCLOPHOSPHAMIDE	Verre	NaCl 0.9%	0.4 mg/mL	14 days at 2–8°C protected from light	49
	PVC	Dextrose 5% or NaCl 0.9%	1 mg/mL	7 days at 4°C and at room temperature protected from light	50, 51
CYTARABINE	PVC	NaCl 0.9%	0.018 mg/mL	29 days at 23°C or 2°C	52
	Ethyl vinyl acetate	Dextrose 5% or NaCl 0.9%	1.25 and 25 mg/mL	28 days at 25°C or 4°C protected from light	53
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	54
	PVC	Dextrose 5%	1.5 mg/mL	7 days at 4°C and 3 days at room temperature protected from light	
	PVC – polyethylene	NaCl 0.9%	0.640 mg/mL	2 days at room temperature in the light and at 4°C	
DACTINOMYCIN	PVC	Dextrose 5%	0.01 mg/mL	24 hours in the light and at room temperature	55
DAUNORUBICIN At concentrations > 0.5 mg/mL daunorubicin is not photosensitive for at least 7 days	PVC	Dextrose 5% or NaCl 0.9%	0.1 mg/mL	43 days at –20°C, 4°C and 25°C	56, 57
	Polypropylene	WFI	2 mg/mL	43 days at 4°C	
DAUNOXOME				Follow SmPC	
DEXRAZOXANE	PVC	Ringer lactate	4 and 8 mg/mL	8 hours at 25°C in the light	58
	Polyethylene	Ringer lactate	8 mg/mL	8 hours at 25°C in the light	
	Polyethylene	Ringer lactate	4 mg/mL	4 hours at 25°C in the light	
DOCETAXEL *Two vials* After reconstitutions: 10 mg/mL Avoid PVC containers	Glass	Special solvent	Reconstituted: 10 mg/mL	28 days at 2–8°C and at 25°C	59
	Polypropylene – polyethylene	NaCl 0.9% or dextrose 5%	0.3–0.9 mg/mL	28 days at 25°C protected from light; 56 days at 25°C, 2–8°C protected from light	59, 16
DOCETAXEL *One vial* Solution at 20 mg/mL Avoid PVC containers	Polyolefin	NaCl 0.9% or dextrose 5%	0.24 > 1 mg/mL	28 days at 20°C, 5°C protected from light	17

(*Continued*)

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Table 1: SFPO and ESOP recommendations for the practical stability of anticancer drugs (*Continued*)

Product	Container	Vehicle	Concentration	Recommended storage conditions	References
DOXORUBICIN At concentrations > 0.5 mg/mL doxorubicin is not photosensitive for at least 7 days	Polypropylene	NaCl 0.9%	1–2 mg/mL	124 days at 4°C and 23°C	60
	PVC	Dextrose 5% or NaCl 0.9%	0.1 mg/mL	24 days at 25°C and 43 days at 4°C or -20°C	56, 57
EPIRUBICIN At concentrations > 0.5 mg/mL epirubicin is not photosensitive for at least 7 days	Polypropylene	NaCl 0.9%	1–2 mg/mL	150 days at 23°C and at 4°C	61
	PVC	Dextrose 5% or NaCl 0.9%	0.1 mg/mL	20 days at 25°C and 43 days at 4°C or -20°C	56, 57
ERIBULINE MESYLATE	Polypropylene	None	440 µg/mL	14 days at 4°C or 20°C with or without protected from light	32
	Polyolefin	NaCl 0.9%	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%	0.2 mg/mL	96 hours at < 25°C in the light	62
	Polypropylene	NaCl 0.9%	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	63
	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%	0.04 to 1 mg/mL	21 days at 25°C or at 8°C protected from light	18
FLUOROURACIL	Glass or PVC	NaCl 0.9% or dextrose 5%	1.5 mg/mL	8 weeks at room temperature in the light	64
FOLINATE CALCIUM	Glass	Dextrose 5% or NaCl 0.9%	Reconstituted: 20 mg/mL	4 days at 4°C or 25°C protected from light	65
	Glass or PVC	Dextrose 5% or NaCl 0.9%	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%	1–1.5 mg/mL	4 days at 4°C or 25°C in the light	
FOLINATE SODIUM	Polyethylene	Dextrose 5%	3.2 mg/mL	90 days at -20°C or 30 days at 4°C protected from light	28
FOTEMUSTINE Administer protected from light	PVC	Dextrose 5%	0.2–2 mg/mL	2 days at 4°C and 8 hours at room temperature, protected from light	66, 67

(*Continued*)

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Table 1: SFPO and ESOP recommendations for the practical stability of anticancer drugs (*Continued*)					
GEMCITABINE	Polypropylene syringes	NaCl 0.9%	Reconstituted: 38 mg/mL	35 days at room temperature	68
	PVC	NaCl 0.9% or Dextrose 5%	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%	0.1 mg/mL	28 days at ≤ 25°C protected from light	69
IFOSFAMIDE	PVC	Dextrose 5% or NaCl 0.9%	30 mg/mL	30 days at 4°C protected from light	67
	PVC	Dextrose 5% or NaCl 0.9%	0.6–40 mg/mL	4 days at 4°C or room temperature protected from light	
INTERLEUKIN 2				Follow SmPC	
IRINOTECAN	PVC	Dextrose 5% or NaCl 0.9%	0.4 to 2.8 mg/mL	28 days at room temperature or 2–8°C protected from light	70
LEVOFOLINATE CALCIUM	Polyethylene	Dextrose 5%	1.6 mg/mL	95 days at -20°C and 30 days at 2–8°C	29
MELPHALAN – Dextrose 5% must not be used – The degradation of melphalan increases with the temperature	PVC	NaCl 3%	0.2 mg/mL	48 hours at 4°C and 3 hours at 26°C in the light	71
	PVC, polyethylene	NaCl 0.9%	0.06 mg/mL	24 hours at 4°C and 1 hour at room temperature protected from light	45
METHOTREXATE	Polypropylene syringes	NaCl 0.9%	2.5 mg/mL	7 days at room temperature and at 4°C protected from light	72
	PVC	NaCl 0.9% or dextrose 5%	0.225–24 mg/mL	30 days at 4°C protected from light	73
MITOMYCIN				Follow SmPC	
MITOXANTRONE	Glass bottle	Ready-to-use solution	2 mg/mL	42 days at 4°C and at 23°C	74
	PVC	NaCl 0.9% or dextrose 5%	0.04–0.4 mg/mL	7 days at 4°C and at 23°C protected from light	75
MYOCET				Follow SmPC	
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	31
OXALIPLATIN	Polyolefin bags	Dextrose 5%	0.25 mg/mL	90 days at 4°C protected from light or at room temperature with or without protection from light	19
	Polyolefin bags	Dextrose 5%	0.7 mg/mL	30 days at room temperature protected from light	76

(*Continued*)

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Table 1: SFPO and ESOP recommendations for the practical stability of anticancer drugs (*Continued*)

Product	Container	Vehicle	Concentration	Recommended storage conditions	References
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%	0.3–1.2 mg/mL	4 days at 25°C and 12 days at 5°C protected from light	77, 78
	Polyethylene	NaCl 0.9% or dextrose 5%	0.3 mg/mL	13 days at 2–8°C protected from light	
	Polyethylene	NaCl 0.9% or dextrose 5%	1.2 mg/mL	9 days at 2–8°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%	25 mg/mL	2 days at room temperature and 31 days at 4°C protected from light	79, 80
	PVC bags	NaCl 0.9%	5 mg/mL	28 days at 4°C protected from light	
PENTOSTATIN	Glass	NaCl 0.9%	Reconstituted: 2 mg/mL	3 days	81
	PVC	NaCl 0.9%	0.002–0.02 mg/mL	48 hours at 23°C	
RITUXIMAB	Polyolefin	NaCl 0.9%	1 mg/mL	180 days at 4°C	10
STREPTOZOCIN				Follow SmPC	
TEMSIROLIMUS	Polypropylene	NaCl 0.9%	0.1 mg/mL	3 days at 20°C protected from light 4 days at 2–8°C	35
THIOTEPA	PVC, polyolefin	Dextrose 5%	5 mg/mL	3 days at 4°C and at room temperature in the light	82, 83
	PVC	NaCl 0.9%	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%	0.025, 0.05 mg/mL	28 days at 4°C and at room temperature protected from light	84
	Elastomere	NaCl 0.9% or dextrose 5%	0.01 and 0.05 mg/mL	21 days at 25°C not protected from light	
	PVC	NaCl 0.9%	0.01 mg/mL	7 days at room temperature in the light	
TRASTUZUMAB	Polypropylene	NaCl 0.9%	0.8 mg/mL	180 days at 4°C	14
VINBLASTINE	Glass	WFI	Reconstituted: 1 mg/mL	21 days at 4°C protected from light	85, 86
	Polypropylene	NaCl 0.9% or dextrose 5%	0.02 mg/mL	21 days at 4°C and at 25°C protected from light	
	PVC	NaCl 0.9% or dextrose 5%	0.1 mg/mL	7 days at 4°C protected from light	
VINCRISTINE	Polypropylene	NaCl 0.9% or dextrose 5%	0.02 mg/mL	21 days at 4°C and at 25°C protected from light	85, 87, 88
	PVC – polypropylene	NaCl 0.9%	0.01 to 0.15 mg/mL	7 days at 4°C protected from light	

(*Continued*)

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Table 1: SFPO and ESOP recommendations for the practical stability of anticancer drugs (*Continued*)					
	Polyolefin	NaCl 0.9%	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	85
	Polypropylene	NaCl 0.9% or dextrose 5%	0.02 mg/mL	21 days at 4°C and at 25°C protected from light	
VINORELBINE	PVC, polyethylene	NaCl 0.9%	0.385 mg/mL	7 days at 23°C	86, 89
	PVC	Dextrose 5%	0.5 mg/mL	7 days at 4°C	

NaCl: sodium chloride; PVC: polyvinyl chloride; SmPC: summary of product characteristics; WFI: water for injection.

practices in classified rooms. Biological safety cabinet or isolators have to be used for 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 greatly affect 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).

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Cytotoxic surface contamination during automated compounding

Surface contamination with cytotoxic drug substances 5-fluorouracil and platinum containing drugs was investigated during automated preparation with APOTECAchemo and during manual preparation. The contamination levels during robotic preparation were similar or lower than during manual preparation.

Introduction

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The preparation of ready-to-administer cytotoxic drug solutions implies the occupational risk of exposure to cytotoxic drug components in the workplace. Contamination of the workplace can occur indirectly by aerosolized drug product or directly by contact. Various anticancer drugs are known to have carcinogenic, mutagenic or teratogenic properties, so operator exposure should be kept as low as possible. In general, the preparation of ready-to-administer cytotoxic drugs is performed by pharmacy staff in cytotoxic safety cabinets or isolators with laminar airflow. Many studies have been published in the past decade dealing with the occupational exposure of pharmacy staff during compounding of anticancer drug preparations [1]. Working with a robotic system offers a possible route to reducing this risk. However, earlier work found that surface contamination with cytotoxic drugs during automated preparation could be similar or even higher than during manual preparation.

The main goal of this study was to compare the magnitude of surface contamination with cytotoxic drug substances during automated preparation with APOTECAchemo—a robotic system developed by Loccioni Humancare, see photo below; and during manual preparation in a dedicated clean room facility.

Materials and methods

The contamination level of five predetermined surface areas with a high contamination risk inside the APOTECAchemo cabinet was investigated with wipe tests using a proven method [2-5]. The five sampling surface areas inside the working area of the APOTECAchemo cabinet are, see Figure 1 included the:

1. Surface of the balance, where the bags and vials are weighed
2. Surface area under the shelves, where the drug vials are stored temporarily
3. Syringe holder, close to where the cytotoxic drug solutions are withdrawn from the vials into the syringes before being injected into the bags
4. Surface area beneath the syringe holder
5. Gripper of the robotic arm, which operates all components during the compounding process

During the study, 5-fluorouracil (5FU) and platinum-containing cytotoxic drug products—cisplatin, carboplatin and oxaliplatin—were prepared with APOTECAchemo on two consecutive days. Prefilled 500 mL bags (Freeflex, Fresenius) were used as vehicle solutions and primary packages.

In total, 15 bags containing 5FU and 15 bags containing platinum derivatives were prepared, i.e. 15 x 5FU 1200 mg in a final volume of 500 mL solution 0.9% NaCl solution (day one), 5 x cisplatin 40 mg in a final volume of 500 mL 0.9% NaCl solution (day two), 5 x carboplatin 450 mg in a final volume of 500 mL glucose 5% solution (day two), 5 x oxaliplatin 120 mg in a final volume of 500 mL glucose 5% solution (day two). The doses and concentrations of the cytotoxic drugs were chosen to represent the lowest doses compounded for patients in our pharmacy-based cytotoxic preparation unit.

The wiping kits and instructions for on-site wiping were provided by the Institute for Occupational, Social and Environmental Medicine, Ludwigs-Maximilian-University Munich, Germany. The predetermined surface areas in the working

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area of APOTECAchemo were wiped before and after the preparation process at day one and day two. In addition, the outer surface of each bag prepared was wiped. Typically an area of 400 cm² (20 cm x 20 cm) was sampled with a moistened wipe filter. If not feasible, the sampled area was measured exactly and the size documented. Each filter was transferred to a glass container and capped.

In parallel, the surface contamination during manual preparation in a cytotoxic safety cabinet was tested. Fifteen bags containing 5FU and 15 bags containing platinum derivatives were prepared manually by an experienced technician over two consecutive days. The prepared products were identical in formulation and quantity to those prepared with the robotic system.

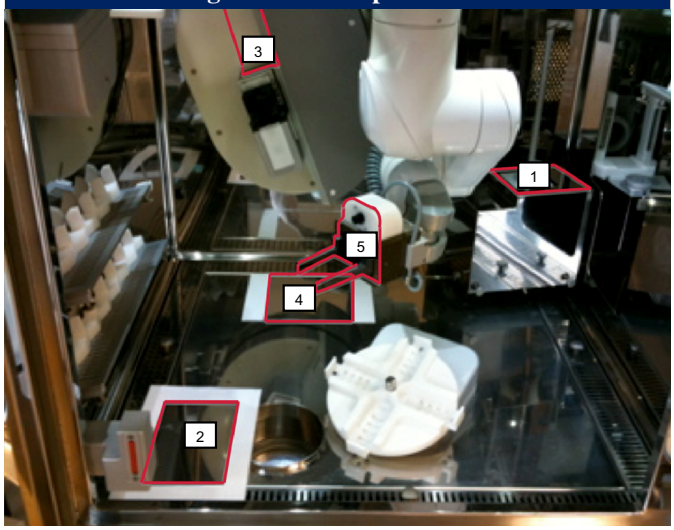
The four predetermined sampling areas inside the cytotoxic safety cabinet (Berner FlowSafe C-[MaxPro]^{3}–130) are:

- Single-use, waterproof mat on which the preparation process is performed
- Single-use, waterproof mat where the drug vials are temporarily stored
- Surface area at the right site of safety cabinet where the items needed for preparation are introduced and temporarily stored
- Surface area at the left site of safety cabinet where the products and waste are temporarily stored

Sampling on the predetermined surface areas was done before and after the preparation process. The outer surface of the gloves worn during preparation by the technician was wiped all over before and after preparation using the same method. In addition, the outer surface of each prepared bag was sampled.

The samples were kept refrigerated (4°C) and sent overnight to the Institute for Occupational, Social and Environmental Medicine, University of Munich, Germany for analyses. All 5FU suspect samples were analysed by gas chromatography/mass spectrometry. The platinum suspect samples were analysed by inverse voltammetry [2]. The total amount of 5FU or platinum was determined per sample. For surface area and glove samples the results were reported in pg/cm².

Figure 1: The five sampling surface areas inside the working area of the Apoteca cabinet



The results were evaluated according to the threshold guidance values (TGVs) for surface monitoring, see Table 1. These were developed for 5FU and platinum by Schierl et al. [3] by statistical analysis of a large dataset of monitoring results in German pharmacies. So far no occupational threshold limits for acceptable levels of cytotoxic contamination according to the toxicological risk are defined. As a practical alternative, the guidance values allow a categorization of the surface load with the cytotoxic drugs and presentation according to the traffic-light principle.

Results and discussion

From the 10 samples taken in the working area of APOTECAchemo and analysed for 5FU contamination, seven results were categorized in the green TGV category and three results in the red TGV category. From the 10 samples analysed for platinum contamination, eight results were categorized in the yellow TGV category and two results in the red TGV category, see Table 2. The high-level contamination with 5FU and platinum in the working area of the APOTECAchemo cabinet was even evident after cleaning and before starting the compounding process. The contamination could either derive from external drug vial contamination or from inaccurate handling of the vials. In the last case, the spreading of cytotoxic drug substances can occur during the withdrawal process from the vials to the syringes and/or from the injection process from the syringes into the bags. These are the most critical phases of the automated compounding process. During these process steps, aerosols and droplets of the cytotoxic solution could be released, especially if pressure equalization is not achieved. The setting of the parameters that control each individual operation of the robotic arm is of vital importance to minimize these phenomena.

Unsurprisingly, the highest levels of contamination in the working area were found on the syringe holder and on the gripper. The former represents the location where the cytotoxic drug solutions are transferred via a vented needle. The latter is the only robotic part that continuously touches the external surface of the drug vials. The levels of contamination found by wipe sampling on the other predetermined surface areas, and especially on the outer surface of the bags during automatic

Table 1: Threshold guidance values for surface monitoring [3]

Results of all samples	5FU (pg/cm²)	Platinum (pg/cm²)
Better than 50%	≤ 5.0	≤ 0.6
Between 50% and 75%	≤ 30.0	≤ 4.0
Worse than 75%	> 30.0	≤ 4.0

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Table 2: Surface contamination in the working area of the APOTECAchemo cabinet before and after compounding

Place of sampling	5FU (pg/cm²)	Platinum (pg/cm²)
Before compounding		
Balance (ca. 45 cm²)	nn	2.6
Floor under the shelves (ca. 270 cm²)	3.0	2.7
Syringe holder (ca. 400 cm²)	2.8	14.4
Floor under the syringe holder (ca. 400 cm²)	nn	1.4
Robotic arm (ca. 180 cm²)	58.3	3.2
Blank value	–	–
After compounding		
Balance (ca. 45 cm²)	nn	0.9
Floor under the shelves (ca. 270 cm²)	0.7	1.9
Syringes' holder (ca. 400 cm²)	625.0	6.2
Floor under the syringes' holder (ca. 400 cm²)	nn	1.1
Robotic arm (ca. 180 cm²)	4,933.30	1.8
Blank value	–	–

nn: not detected; limit of detection: 5FU = 0.2 ng/sample; platinum = 0.02 ng/sample.

compounding, were low relative to the TGVs or even not detectable, see Table 2.

From the 10 samples taken during manual compounding and analysed for 5FU contamination, seven results were categorized in the green TGV category and three results in the red TGV category. From the 10 samples analysed for platinum contamination, five results were categorized in the green, three in the yellow, and two in the red TGV category (results not shown in detail). The highest levels of contamination during manual preparation in the cytotoxic safety cabinet were found on the mat used for the compounding, on the mat used for the intermediate storage of drug vials, and on the technician's gloves. The results were not unexpected, as external contamination of the vials delivered from the pharmaceutical industry is well known [4]. In addition, a droplet of concentrated 5FU solution (50 mg/mL) that the technician had seen fall on the mat during the compounding process had caused the high level of contamination detected in the wipe sample. The levels of contamination found on the outer surface of the bags manually prepared were generally low and middle according to the TGV classification, although two bags containing platinum derivatives showed a high level of contamination (red TGV).

Overall, the levels of contamination with 5FU and platinum were lower during automated preparation with APOTECAchemo than during manual preparation in the cytotoxic safety cabinet. The risk of contamination remained localised and segregated inside the robotic working area. The outer surfaces of the prepared drug products were marginally contaminated with 5FU or platinum, see Table 3.

Conclusion

The detected cytotoxic contamination levels during automated preparation were similar to or lower than contamination levels during manual preparation. This suggests that automation of cytotoxic drug preparation can reduce the contamination risk. The key factor associated with reduced contamination risk during automated preparation of cytotoxic drugs is the accurate technical validation of the compounding process. Despite this, it is almost impossible to avoid any surface contamination, so a good and reliable cleaning method must be regularly performed to remove any potential surface contamination of the robotic system.

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Table 3: Contamination on the outer surface of the bags during automatic compounding in the APOTECAchemo cabinet

Place of sampling (ca. 400 cm²)	5FU (pg/cm²)	Place of sampling (ca. 400 cm²)	Platinum (pg/cm²)
Bag 1 5FU	nn	Bag 1 cisplatin	0.1
Bag 2 5FU	0.5	Bag 2 cisplatin	0.4
Bag 3 5FU	nn	Bag 3 cisplatin	0.0
Bag 4 5FU	1.0	Bag 4 cisplatin	0.2
Bag 5 5FU	nn	Bag 5 cisplatin	0.1
Bag 6 5FU	0.5	Bag 6 carboplatin	0.0
Bag 7 5FU	nn	Bag 7 carboplatin	0.0
Bag 8 5FU	nn	Bag 8 carboplatin	0.0
Bag 9 5FU	nn	Bag 9 carboplatin	0.1
Bag 10 5FU	nn	Bag 10 carboplatin	0.2
Bag 11 5FU	8.8	Bag 11 oxaliplatin	0.6
Bag 12 5FU	nn	Bag 12 oxaliplatin	0.0
Bag 13 5FU	1.3	Bag 13 oxaliplatin	0.0
Bag 14 5FU	nn	Bag 14 oxaliplatin	0.1
Bag 15 5FU	0.5	Bag 15 oxaliplatin	0.0
Blank value	–	Blank value	–

nn: not detected; limit of detection: 5FU = 0.2 ng/sample; platinum = 0.02 ng/sample.

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Drugs and their costs in the last six days of life: a retrospective study

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Abstract

Introduction and aims: Palliative care provides many advantages to dying patient. In the last days of life five most common predictable symptoms may occur: pain, nausea and vomiting, restlessness, dyspnoea and respiratory tract secretions. Essential medicines should be prescribed in advance to alleviate these symptoms. The purpose of this retrospective study was to determine which drugs patients received in palliative care in the last six days of life compared to terminally ill patients treated standardly and evaluate what was the difference in costs for drugs between these two groups of patients.

Patients and methods: Twenty-five patients were included in the palliative treatment pathway, whereas 25 were treated according to standard treatment pathway and served as a control group. Both groups were comparable by the primary tumour site and median age of patients.

Results: Majority of patients in both groups received strong opioid analgesics. Other drugs to relieve symptoms, such as haloperidol, midazolam, dexamethasone, butylscopolamine and metoclopramide, were more likely to be administered in the palliative group. Polypharmacy was a common problem observed in both groups. However, patients treated according to palliative treatment pathway received on average 10 drugs, whilst those in control group 14. The costs for drugs were 2.7-fold lower in the palliative group, Euros 15 compared to Euros 42 per patient per day.

Conclusion: The main goal of palliative care is to ensure the good quality of life of terminally ill patients, so we need to find a balance between necessary and unnecessary drug treatment.

Keywords: Costs, drugs, palliative care, terminal phase

Introduction and aims

Palliative care is the active and total care of patient whose progressive disease is not responding to curative treatment. When prolonging life is neither reasonable nor possible, relieving suffering becomes more important than efforts to preserve life. The goal of palliative care is to achieve the best possible quality of life for the person in a given situation; therefore, all efforts are directed towards controlling pain and other distressing symptoms, and alleviating psychological, social and spiritual problems.

Society's attitude towards dying and death affects the development of palliative care to a large extent. Palliative care has already become part of everyday clinical practice in the western world, whereas, in Slovenia, for example, it is just beginning. A pilot project to implement an integrated palliative care programme took place in three Slovenian regions from June 2009 to October 2010 by order of the Ministry of Health. The programme was evaluated from a professional, personnel, organizational and financial perspective. The financial indicator was also the drugs used in the last six days of life.

The main aim of palliative care is to ensure a good quality of life for terminally ill patient. In order to do so, a balance needs to be achieved between necessary and unnecessary drug treatment. The purpose of this retrospective study was to identify differences in the use of drugs among terminally ill patient in palliative care and patient treated according to a standard protocol (control group).

Patients and methods

The trial included 50 patients with incurable advanced cancer who died at the Institute of Oncology in 2010, with a last stay in hospital of at least six days. Twenty-five patients were allocated to a palliative care group, and 25 patients to a control group. Patients in both groups had comparable diagnoses and ages, for each person in the palliative care group, a similar aged person (within the same decade) with the same primary cancer was allocated to the control group, see Table 1.

For each individual, the quantity of drugs received in the last six days of life was counted, with a day of death marked as day one. The treatment was evaluated financially by the pharmacy computer programme.

Results

The total cost of drugs received by the 50 patients in the last six days before death were Euros 8,654, of which Euros 2,324 were used for patient in the palliative care group; and the remaining Euros 6,330 for patient in the control group, see Table 2. The average cost of drugs for one person in the palliative care group was Euros 15 per day and Euros 42 per day for one person in the control group, see Figure 1. The difference was also seen in the number of medications: patients received an average of 10.1 medications in the palliative care group and 14.1 medications in the control group, see Table 2.

The most frequently prescribed drugs for patients with advanced disease were analgesics. Most patients in both groups were

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Table 1: Distribution of patients

Primary tumour sites	Palliative care group (n)	Control group (n)
Kidney, bladder	7	7
Breast	4	4
Colon, rectum	3	3
Pancreas	3	3
Malignant melanoma	2	2
Throat, oesophagus stomach	2	2
Uterus	1	1
Peritoneum	1	1
Brain	1	1
Lungs	1	1
Total	**25** (9 men and 16 women)	**25** (11 men and 14 women)
Average age (years)	65.6 (43–83)	65.2 (40–82)

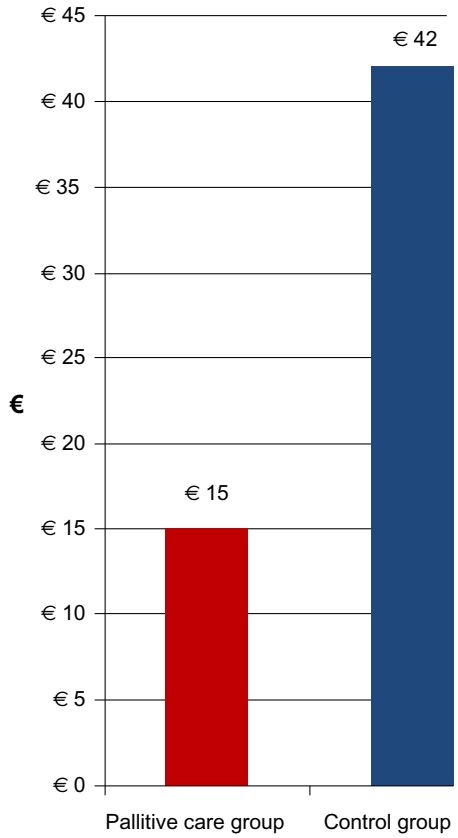
prescribed strong opioids, see Figure 2. Five patients in each group (20%) had a continuous subcutaneous infusion using an elastomeric pump. One person in the palliative group received an analgesic mixture via epidural catheter.

Haloperidol, midazolam, dexamethasone, butylscopolamine and metoclopramide are drugs routinely used to relieve distressing symptoms before death, and were prescribed in slightly greater quantitites to patients in the palliative care group, see Figure 3. More patients in the control group received weak opioids and non-opioids, proton pump inhibitors, low molecular weight heparins, systemic antibiotics and antifungals, and parenteral nutrition, see Figure 2. The last two drug classes represent the largest cost difference between the two groups of terminally ill patient, see Figure 4.

Table 2: Cost and number of drugs given to terminally ill patients

	Palliative care group	Control group
Number of participants	25	25
Cost for drugs over six days	Euros 2,324	Euros 6,330
Cost for drugs over six days per person	Euros 93 (Euros 7 – Euros 244)	Euros 253 (Euros 23 – Euros 1,180)
Average cost for drugs per person per day	Euros 15	Euros 42
Number of medicinal registered products per person	11.7 (4–20)	15.6 (6–41)
Number of drugs per person	10.1 (3–15)	14.1 (6–35)

Figure 1: Average cost of drugs per patient per day



Discussion

The physician's duty is always to act in favour of the patient. Although death is an integral part of life, we still tend to delay it. Medical obligation to preserve a person's life should end when the disease process leads to death irreversibly. Actions for prolongation of life are rightly omitted, as the prolongation of life in such situations is a source of additional

Figure 2: Most frequently prescribed drug classes

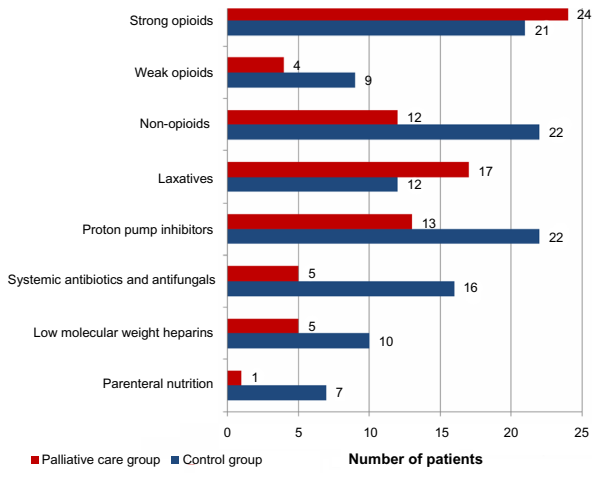


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Figure 3: Frequency of prescribing essential medicines in addition to analgesics

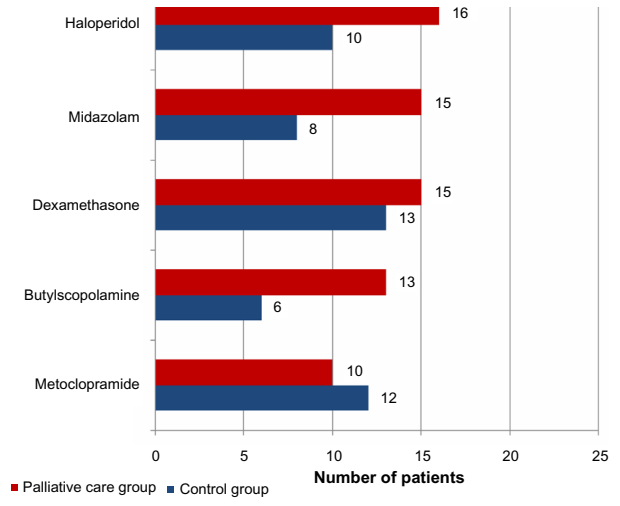
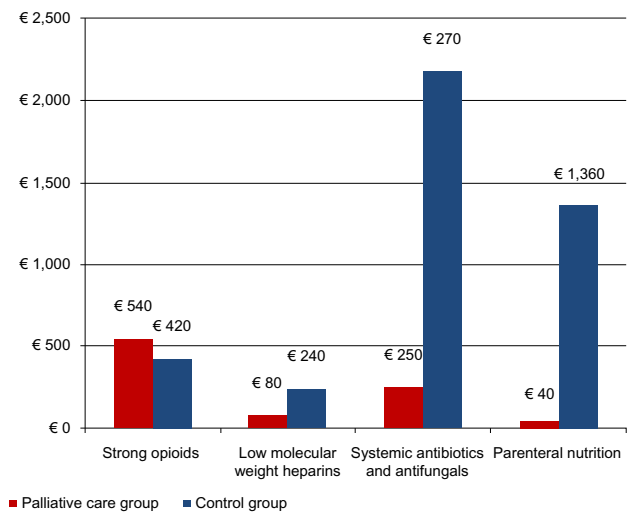


Figure 4: Cost differences for some drug classes



suffering and is not compatible with human dignity and human values. In this case, palliative care is the option of choice.

The biggest advantage of palliative medicine is improving the quality of treatment of patient with advanced incurable chronic disease. Improved quality of the last days of life will be achieved if symptoms that usually occur in the phase of dying pain, nausea and vomiting, agitation, dyspnoea, respiratory tract secretions) are alleviated, and thus essential drugs become analgesics, antiemetics, sedatives, anxiolytics and anticholinergics. If necessary, a route of administration should be replaced. All unnecessary medicines, such as antibiotics, antidepressants, laxatives, antiarrhythmics, anticoagulants, and vitamins, should be omitted.

The changes in treatment must be explained to the patient and relatives, who sometimes do not understand why that person has stopped taking a medicine they have used in recent years.

Dying patients often suffer from severe pain. In palliative medicine, where pain grows rapidly because of disease progression, a strong opioid can be introduced without prior use of weak opioids. Strong opioids were given to more than four out of five terminally ill patients in the study (96% in the palliative care group and 84% in the control group. Four patients (16%) in the palliative group were treated with weak opioids and 12 patients (48%) with non-opioid analgesics. In the control group, however, nine patients (36%) had weak opioids, and as many as 22 patients (88%) had non-opioid analgesics.

Transdermal fentanyl or buprenorphine patches were used by nine patients in the palliative care group (36%) and five patients in the control group (20%). These patches are a good substitution for morphine in patients who would require a stable dose of oral morphine. Strong opioids with shorter duration of time are more suitable for patients in the terminal stage of a disease because the condition of the person and the severity of pain may be changing rapidly and requires immediate dose adjustment.

Patients with persistent nausea and vomiting, dysphagia, or impaired consciousness, receive morphine by continuous subcutaneous infusion using elastomeric pump. The advantage of this application is the possibility of adding other drugs into the analgesic mixture, so multiple symptoms with a combination of drugs can be controlled. In this study, five patients (20%) in both the palliative care group and the control group had their pain regulated by continuous subcutaneous infusion in elastomeric pump. One person (4%) in the palliative group received an analgesic mixture via epidural catheter.

Prophylaxis of side effects of opioids is also important; antiemetics are used when opioid treatment and laxatives are introduced and are used in conjunction throughout the treatment period. Constipation refers to infrequency or difficulty in defecation of small amounts of hard stool. In patients receiving strong opioids, the concomitant use of stimulant laxatives should be the rule rather than exception. Senna is a potent contact laxative that can be combined with stool softener (lactulose). In the last six days of life, laxatives were administered to 17 patients in the palliative care group (68%), of which two patients needed methylnaltrexone Relistor. In the control group, 12 patients (48%) received laxatives.

For prevention and treatment of peptic ulcer disease caused by non-steroidal anti-inflammatory drugs, proton pump inhibitors are used. They were given to 13 patients (52%) in the palliative care group and to 22 patients (88%) in the control group.

In addition to pain, nausea and vomiting are the most common symptoms in patients with advanced disease. Metoclopramide

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is a prokinetic and antiemetic drug that blocks D2 receptors in chemoreceptor trigger zone. Prokinetics are first-line medicines for nausea owing to gastritis, gastric stasis, and delayed gastric emptying. Metoclopramide should not be used in patients with gastrointestinal obstruction, colics or diarrhoea. The number of patient in the study treated with metoclopramide was comparable in both groups: 10 patients (40%) in the palliative group and 12 patients (48%) in the control group. 5-HT3 antagonists are generally not used in palliative medicine because of constipation; however, one person in each group received granisetron.

Haloperidol is a neuroleptic that acts via D2 receptors in chemoreceptor trigger zone. It is the first-line antiemetic in patients with gastrointestinal obstruction, nausea and vomiting owing to biochemical causes hypercalcaemia, renal failure or medications (opioids). Because of sedative properties, it is used in the agitated terminal delirium. Haloperidol was received by 16 patients (64%) in the palliative care group and 10 patients (40%) in the control group.

Midazolam is a short-acting benzodiazepine used in terminal agitation (with anxiety in forefront), palliative sedation, muscle spasms, epilepsy and dyspnoea. Dyspnoea or breathlessness is a subjective experience of breathing discomfort, and is frightening for both patients and their relatives. In order to alleviate shortness of breath in a person at rest, low-dose morphine is most often used; anxiolytics can also help (benzodiazepines in particular), as a panic fear worsens dyspnoea. Midazolam was given to 15 patients (60%) in the palliative care group and eight patients (32%) in the control group.

Butylscopolamine (hyoscine butylbromide) is an anticholinergic agent and has antispasmodic and antisecretory properties. It reduces secretions of the gastrointestinal tract and therefore prevents vomiting in gastrointestinal obstruction. Butylscopolamine competitively blocks the prokinetic effect of metoclopramide, so concomitant treatment should be avoided if possible. Butylscopolamine is also used to reduce death rattle in a dying person by drying bronchial secretions. In our study, butylscopolamine was given to 13 patients in the palliative care group (52%) and only six patients (24%) in the control group.

Corticosteroids are adjuvant analgesics used to treat pain caused by oedema, and they are antiemetics and appetite stimulators. Dexamethasone is the corticosteroid of choice in palliative medicine, as it causes less fluid retention compared with methylprednisolone. More than one-half of terminally ill patients in each study group received dexamethasone over the last six days: 15 patients (60%) in the palliative care group and 13 patients (52%) in the control group.

With the above-listed medicines, five of the most common symptoms in dying patients that may develop in the last hours or days before death can be controlled. These are pain, nausea and vomiting, agitation, dyspnoea and respiratory tract secretions [1, 2]. It is important to predict the symptoms and prescribe the drugs in advance. Drugs for symptom control should only be given when required. The dose should be no more than is needed to control the symptom and should be titrated according to patient need [3]. The essential drugs for symptom control were available to all study participants; the only difference was the proportion of patients who received these drugs. The pain was controlled well in both groups, but other drugs were prescribed more frequently in the palliative care group.

The biggest difference between the groups was seen in low molecular weight heparins, systemic antibiotics, antifungal agents, and parenteral nutrition. They are no longer useful in the terminal phase, and should be omitted because the artificial prolongation of life brings only additional suffering to a terminally ill patients [4]. These drugs were also received by two patients in the palliative care group, but the prescribing was significantly higher in the control group. Low molecular weight heparins were administered to five patients (20%) in the palliative care group and 10 patients (40%) in the control group over the last six days before death. Thromboprophylaxis may prevent significant symptoms (dyspnoea, leg swelling/pain) in terminally ill patients, but otherwise it should be discontinued when the reversible causes are excluded and the disease has progressed to such an extent that it leads to death irreversibly [5-8].

Systemic antibiotics and antifungals were administered to five patients in the palliative care group (20%) compared with 16 patients (64%) in the control group. Hospital reserve antibiotics were prescribed to nine patients (36%) in the control group (piperacillin and tazobactam, vancomycin, cefepim, ertapenem, and imipenem and cilastatin). The aim of a course of antibiotic should be considered carefully and individually for every patient. A decision not to commence treatment for infection or withdrawing treatment is always difficult and varies from case to case. Patients in the last few days of life may not respond symptomatically to antibiotics, and potential side effects need to be considered [4, 9].

One person (4%) in the palliative group and seven patients (28%) in the control group received parenteral nutrition. Studies show that assisted nutrition does not improve symptoms and does not affect the length of survival. Starvation in the terminal phase has a positive effect because ketoacidosis leads to release of endorphins. Similarly, parenteral hydration in the terminal phase is not beneficial because it can worsen oedema, dyspnoea, respiratory tract secretions, and nausea and vomiting. Dehydration causes a release of endorphins through uraemia and hyperosmolarity, and thus causes patient suffering. All decisions to discontinue, continue or commence the use of assisted nutrition and hydration must be made in the best interests of each individual [2, 10].

The last two groups of drugs (systemic antibiotics and antifungals, and parenteral nutrition) represent the biggest financial

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burden in the control group, as costs account for more than one-half of total drug costs.

Polypharmacy and inappropriate use of drugs are widespread in the last days before death. Dangers from drug interactions, and also concomitant use of more drugs, increases the chance of adverse drug reactions and decreases patient compliance with medications. Patients treated with standard care received an average of 14.1 different drugs compared with 10.1 drugs received by patients in the palliative care group. This value is similar to the results of a study conducted in Canada, in which terminally ill patients throughout their stay in an acute palliative department received an average of 10.5 drugs [11]. Clinically significant interactions have been found in more than one-fifth of hospitalized patients who received 10–20 drugs concomitantly [11].

Long-term acting drugs, and drugs that produce no complications owing to withdrawal, may be discontinued in the terminal phase while keeping the patient under observation. Cardiovascular drugs are seldom needed because the heart is under less strain, as advanced malignant disease itself lowers blood pressure, removing the need for antihypertensives. The positive effects of statins, i.e. reduced cardiovascular disease mortality, are evident only after many years of administration. In patients who are terminally ill, the benefits of statins are negligible, as the rest of their lives are determined by incurable disease, but the risk of serious adverse reactions and drug interactions is high. Hypoglycaemic drugs may be discontinued in terminally ill patients, in patients with type 2 diabetes, food intake is so small in the last days that hypoglycaemic drugs are not called for [12, 13]. Each drug and its original indication should be reviewed in this way, and a decision of whether or not it will be useful in these last moments (or will only enhance and prolong suffering) must be made.

Conclusion

Five main symptoms may develop in the last hours or days of life. In this retrospective study, we found that pain was controlled well in both groups of terminally ill patients, whereas other symptoms, e.g. nausea and vomiting, restlessness, dyspnoea and respiratory tract secretions, were better controlled in the palliative group. Patients in the palliative care group received more butylscopolamine, midazolam, haloperidol and laxatives compared with non-opioid analgesics, proton pump inhibitors, low molecular weight heparins, systemic antibiotics, and antifungal drugs and parenteral nutrition in the control group. Costs for drugs in the palliative group over the last six days were 2.7-fold lower than that for patients receiving standard care. The difference in costs were the result of prescribing low-molecular-weight heparins, systemic antibiotics, antifungal drugs, and parenteral nutrition.

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Development of a quinine test for improved handling of cytotoxic preparations

Gwenaëlle Baussant, PharmD; Constance Georgel, PharmD; Fanny Loeuillet, PharmD; Valérie Paix, PharmD; Bruno Frimat, PharmD; Christelle Fournier, PharmD

Abstract

Introduction/Study Objectives: A simple and rapid quinine test was developed to identify the presence and origin of cytotoxic contamination in a centralized cytotoxic reconstitution laboratory.

Methods: The test covered all levels of the preparation process. Quinine fluorescence is revealed under a UV lamp. Results were analysed and corrective measures taken to improve operator handling and staff training to preserve environmental and staff safety.

Results: Non-sterile vials containing a quinine-acidified solution were prepared to replace the cytotoxic. Twelve successive preparations were realized by 10 preparation technicians: pockets prepared with spikes and needles; and syringes. Analysis of finished preparations and necessary equipments reveal contamination traces on gloves, internal and external thread of the luer lock counterpart, stopper syringes. The location and the kind of contamination allowed us to understand the risky production steps. Our practices were reviewed: the importance of the connect Z rinsing; the adjustment of the syringe volume to flush the luer; and increasing of gloves change frequency.

Discussion/Conclusion: This study shows that despite of the training of technicians, there are critical contamination points. The limitation of our study is the lack of contamination quantification. However, test results are sufficient to modify our manipulation process. The handlers were aware of the importance of the quality of their actions. Manipulations have been revised with the manipulators.

The quinine test is realized initially upon hire, and then annually, in addition to the media fill test.

Keywords: cytotoxic contamination, handling, quinine test

Introduction

Several studies have shown the presence of cytotoxic contamination on the outer surface of vials of anticancer drugs delivered to hospitals, finished preparations, gloves, and on surfaces [1, 2]. The main routes of exposure are dust inhalation, spraying, hand contact with the mouth, and percutaneous entry from touching surfaces or contaminated objects [3].

In several studies, the presence of cytotoxic in the urine of nurses and pharmacy personnel involved in the administration of therapy was analysed. On the basis of these results, a central pharmacy preparation service has been introduced, the personnel no longer has any trace of cytotoxic detected in their urine [4, 5].

Acute symptoms were observed in cases in which the handler was insufficiently protected. These included dermatitis and local toxic or allergic reactions in direct contact with the skin or mucous membranes, abdominal pain, vomiting, hair loss, and headaches [6].

As a result of the many toxic effects that can occur from exposure to cytotoxic drugs, it is important to develop strategies to protect staff. A three-step approach involves educating and training staff, environmental control and adherence to safe working procedures [7].

The cytotoxic reconstitution system must meet three quality criteria: the quality of the preparation; the quality of the protection of the handler; and the quality of environmental protection. The establishment of protective equipment, such as laminar flow systems or isolators, strict adherence to safety guidelines, and organizational measures, have significantly enhanced the safe handling of cytotoxic agents and environmental protection [8, 9].

In general, centralized pharmacy preparation has increasingly gained ground over decentralized preparation, and standards have been established at least at the national level in France by the evaluation and research group about protection in controlled atmosphere (*Groupe d'Evaluation et de Recherche sur la Protection en Atmosphère Contrôlée)*, and the French Society of Oncology Pharmacy (*Société Française de Pharmacie Oncologique)*. Cytotoxic preparation has basic requirements for personnel training and evaluation in manipulation skills.

Within the pharmacy of the *Centre Hospitalier de Lens*, injectable cytostatic drugs are prepared centrally in negative pressure isolators, with an input and an output airlock under sterile conditions. Pharmacists working in negative pressure can be protected from possible dispersion of agents in the environment prepared in breach of the separation barrier. Two isolators (class A) are situated in a controlled atmosphere zone that is class C. A total of 10,000 preparations are produced each year in the hospital centre, which has two specialties: oncology and haematology.

To ensure safety, this task is always carried out by 10 pharmacy specialized technicians and three pharmacists.

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Given that the potential effect of such contamination on the health of staff working in a centralized cytotoxic reconstitution laboratory is not well understood, the policy in this area should be guided by caution. For this reason, manipulation habits must be optimal to reduce cytotoxic traces of contamination. It is important to identify the origin of the spread of contamination during daily practice.

The quinine test aims to identify the hazards of handling cytotoxic anticancer drugs by identifying traces of contamination so that health care can be controlled and improved.

Study objectives

Our first objective was to develop a simple and rapid method for assessing chemical contamination using a non-cytotoxic chemical marker. The second aim was to analyse the possible location of contamination in the course of the operators' handling, and, if necessary, establish and ensure the efficiency of simple corrective measures aimed at preserving the environment and staff safety.

Materials and methods

The use of markers enables practices to be analysed without posing any risks to the operators or observers. In a review of the literature, we found that solutions of quinine and fluorescein should be appropriate as contamination markers for our practices [10-13]. Quinine presents some advantages, including being colourless. Indeed, with coloured markers, the technician can see the contamination traces in real time. In fact, the operators' manipulations can be affected by the fluorescein's colour. Quinine fluorescence is revealed under ultraviolet lamp. The contamination sites were visible under 386 nm ultraviolet light.

Results

A quinine test was prepared in non-sterile vials containing a quinine-acidified solution to replace cytotoxic vials. In our daily practice, chemotherapy drug preparations are reconstituted from powder in a glass vial or are available as ready-to-use solutions. This is often followed by a dilution. Each opaque glass vial contained 50 mg of quinine hydrochloride powder, 25 mg of citric acid powder per vial, and 10 mL of water for injection.

The addition of citric acid is required to visualize the fluorescence solution. In fact, fluorescence cannot take place without a weak acid. We carried out several different quinine dilutions to observe the best fluorescence. Different quinine concentrations and different quantities of acid were tested to obtain a good fluorescence. We determined the best formulation to visualize contaminations. After preparing vials of quinine, we checked for the absence of quinine solution traces on the outside of the vials.

Quinine test protocol

We developed a protocol to test the handling of a cytotoxic preparation by asking technicians to prepare a safe simulated liquid cytotoxic drug—using syringes, pockets with a prepared quinine solution at the end of their work day according to the pharmacy service's standard operating procedures. The protocol was based on routine manipulations in daily practice. Participants were observed throughout the preparation.

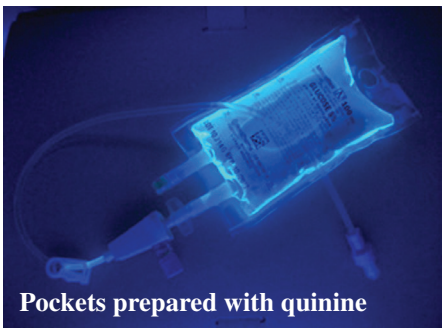
Each technician carried out a series of 12 preparations in total: three pockets were prepared with spikes; three pockets were prepared with needles; three syringes were prepared with spikes; and three syringes were prepared with needles. The chosen diluent was glucose and not sodium chloride, as noticed that sodium chloride neutralized quinine's fluorescence.

The number of preparations produced during the test approximated to one-half of the number of preparations produced during a normal working day. Preparations were carried out on bench in a controlled atmosphere zone (class C). Then, pockets and syringes were placed in the transfer space. The examiner (pharmacist) received preparations at the end of the process. Both the examiner and the technician examined them under ultraviolet light to highlight contamination traces, which appeared blue owing to the fluorescence property of quinine. Each pair of gloves and each care fields were changed after each series of preparations.

Quinine test results in Centre Hospitalier de Lens

Ten operators carried out the test: eight pharmacy technicians and two pharmacists. The test lasted about 1.5 hours.

The search for contamination traces commenced once the operator had completed the preparations. The operator carried out the search and analysis of the results of the completed preparations and necessary equipment. The search for quinine contamination took place at all levels of the preparation process: equipment—spike, needle, connect Z, syringe, pocket outside, sterile field, gloves, pocket packaging, preparation sheet, computer keyboard and storage cases.



Pockets prepared with quinine

Syringes prepared with quinine

Pockets and the inside of syringes were examined under ultraviolet light to prove that quinine had really been used.

Once all the preparations (40 series) had been completed, we found contamination traces localized on the gloves of eight

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technicians (20%). Contamination was found on three gloves in the pockets prepared with needles, on two gloves in syringes prepared with needles, in two gloves in syringes prepared with spikes, and on one glove in the pockets prepared with spikes. Sterile fields were contaminated in seven preparations (17.5%). Contamination occurred in three out of seven pockets prepared with spike, and two out of seven pockets prepared with needles.

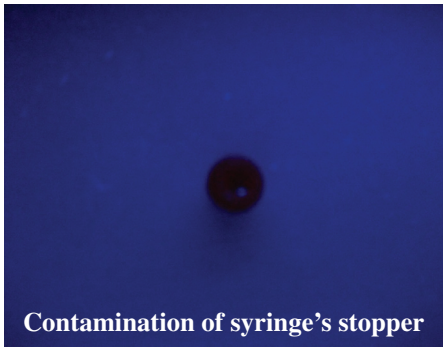
In one-half of pockets prepared with needles, the tip of quinine droplets on the septum was seen at the injection site of the pocket. The internal thread of the connected Z's Luer lock was also contaminated in nine out of 10 pockets prepared with spikes. Contamination on the stopper of the connect Z occurred in six out of 10 preparations.

At the opening of the syringe stopper, quinine droplets were present on the internal and the external thread of the Luer lock counterpart in 30% of cases; 90% of the stoppers were contaminated in syringes that had been prepared with spikes or needles, and 80% were contaminated in cases where the syringes were prepared with spikes.

Syringes prepared with needles required diluent in a pocket. The sampling was achieved with syringes containing a solution of quinine. Fluorescence was found in two out of 10 pockets of diluent. The operators reintroduced quinine in the syringes when they adjusted volume.

No trace of quinine was evident after the clamp inside the tubing of the delivery devices was removed. No traces of contamination were visible on primary packaging, secondary packaging, and labels attached to the pockets and needles, or on the preparation sheet, transparent storage cases, black carrier, or the black computer keyboard. For the carrier and keyboard, quininefluorescence was not visible on the black surface.

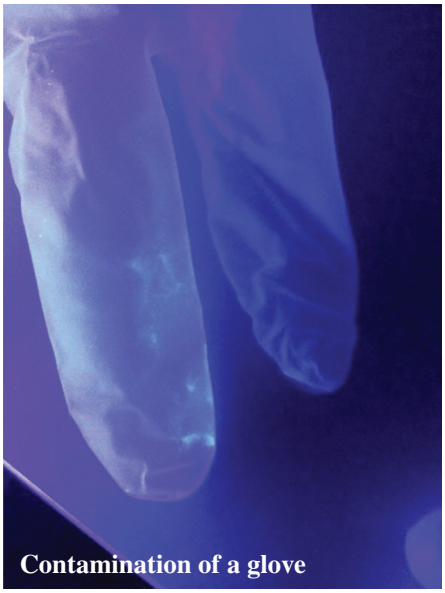
Syringes, thread of the Luer lock counterpart gloves



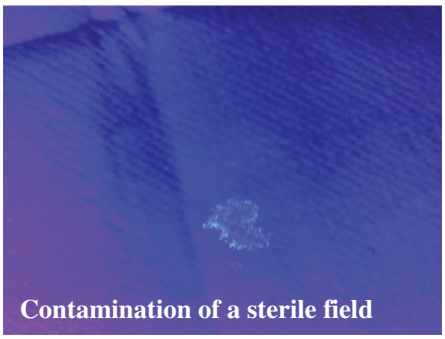
Contamination of syringe's stopper

The techniques of sample and cytotoxic reconstitution used in the quinine test allowed us to see whether cytotoxic reconstitution differed from techniques learned during the initial training programme of technicians.

Divergence in practice exists, and this has led us to evaluate our general practice and particularly the practice of each operator, so that corrective actions can be taken.



Contamination of a glove



Contamination of a sterile field

Once the results of the quinine test had been collated, we reviewed our own practices. Because of the large number of contamination traces found, the first change in practice was to rinse the connect Z. For the pockets prepared with needles, we introduced the procedure of wiping the injection site with a compress to prevent the spread of contamination.

Moreover, we introduced a new practice to minimize contamination caused by nurses at the opening of the syringe by adjusting the syringe volume to flush the Luer lock rather than releasing a droplet over the Luer lock, so that bubbles could be avoided in the syringes during the stopper's closing.

Traces of quinine on the gloves and sterile field may occur at various stages of preparation. Some manipulations, such as the withdrawal of needles, septa vials, transfer of drug using syringes and needles, and the expulsion of the air from the syringe, may cause splashes and sprays. We therefore highlighted the necessity of frequently changing gloves and field because of projections, and the use of sterile compresses when a connection or disconnection takes place.

Pharmacists who are less involved in handling on a daily basis, or pharmacy technicians who are newly trained or handle less frequently, had more contamination during the quinine test. Practical training, particularly in handling, will be stepped up for new manipulators, with the view of increasing handling accuracy. In addition, it was decided that non-cytotoxic drugs would be used in practical training to safeguard newly trained operators and the environment.

As our study shows, the use of syringes or spikes is not determinants of contamination, and that not more contamination

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occurs with syringes than with spikes. So the two techniques will continue to be used in daily practice.

Discussion

An advantage of searching contamination traces in the above way is that the non-toxic marker is invisible except under an ultraviolet lamp. As commercial kits do not exist, we have developed a simple method based on quinine solution that requires standard equipment. Our study requires routine equipment and manipulations similar to daily practices. Each organization should review the type of preparation produced, and adapt their own quinine test to their procedures. The quinine test should be as close as possible in design to the most challenging or stressful conditions that might be encountered during preparations. All employees involved in cytotoxic preparations should participate in the quinine test to ensure best standards of practice. This includes pharmacists who are involved in checking the final product prepared by technicians but who are not involved in handling compound cytotoxic preparations themselves. Pharmacists or technicians that occasionally prepare cytotoxic should also carry out a quinine test. The operators in this study adhered to the quinine test because it raised their awareness of how chemical contamination can occur.

In this study, we found that proximity to daily practice would have helped produce more efficient results. It would have been preferable, for example, to carry out the quinine test in the isolator. This was not possible because the ultraviolet lamp could have contaminated the isolator, and peracetic acid may have damaged the ultraviolet lamp. As we did not wish to evaluate microbiological contamination in our test, manipulation in a controlled atmosphere zone seemed to be the best choice without any interference from our activity.

Also, this procedure does not allow quantitative measurement of traces of contamination, although the technician's exposures to cytotoxic preparations are well known [1, 2]. Qualitative analysis was, however, sufficient to modify our practices.

In the test, operators had not manipulated for a sufficiently long period of time to enable traces of quinine on the storage carrier or the preparation sheet to be observed.

The quinine test was also carried out at the end of the working day. The pharmacy-working environment is stressful, and the requirement to carry out a large number of preparations, each technician produced one-half of their daily preparations, at a time when vigilance was reduced may have been a disadvantage. Two technicians were not evaluated because of time constraints.

This study was successful in identifying risks in the preparation process and adjusting the manipulation process accordingly. It can help operators become more efficient in the preparation process. A review of the results with the technician was a good way of establishing good practices of preparation and identifying practical training if necessary.

Conclusion

Chemical contamination in the field of drugs is a recurrent problem to be investigated. Excessive exposure of all people in contact with active molecules must be avoided. Some toxic drugs may have adverse effects on the health of staff. In this paper, we present a protocol for a quinine test to evaluate operator handling. The experience at the *Centre Hospitalier de Lens* shows that this test is simple and can be easily replicated in other centres. It can be used to analyse daily handling and implement prompt corrective actions. The ultimate goal is to inhibit the spread of cytotoxic contamination and protect the health of staff. At the very least, the quinine test should be used on hiring pharmacy personnel, and annually thereafter. The results of the test clearly showed that lack of training contributed to contamination risks. That is why operator trainings periods and evaluation must be implemented to improve practices. The closed system transfer device has been suggested as an alternative. These are medical devices that prevent the escape of hazardous drugs or vapour concentrations; however, the price of this system is prohibitive and outside the scope of hospital budgets for cytotoxic preparations.

The quinine test is just one, albeit an important, component of a number required for an overall quality assurance programme. The quinine test has been integrated into the annual handlers' validation as well as the media fill test.

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References 7–13 can be found on page 17.

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Is switching taxanes safe?

Aurélie Constans-Brugeais, PharmD; Christelle Lévy, MD; Blandine De La Gastine, MD; Fabienne Divanon, PharmD

The authors report a cross-reactivity rate of 12.5% in patients who had a hypersensitivity reaction with a first taxane (docetaxel or paclitaxel) and were subsequently treated with the second. Caution is required when re-challenge is indicated.

Introduction

Paclitaxel (P) and docetaxel (D) are two commonly used cytotoxic antineoplastic agents belonging to the family of taxanes. The oldest P is extracted from the Pacific yew. Docetaxel arrived later on the market, and is the synthetic analogue of P.

Severe hypersensitivity reactions (S-HSR) to P have been reported despite appropriate premedication. The use of steroids and histamine receptor antagonists reduced the incidence of S-HSRs from 10% to 2% [1].

Docetaxel is sometimes used as an alternative in patients who have developed hypersensitivity to P infusion. Despite this, S-HSRs grades 3 to 4 are also reported with D in 0.6% to 5.3% of cases [2].

The possibility of developing cross-sensitivity between P and D should not be underestimated. Two retrospective studies described cross-reaction in patients who were re-challenged with D after a previous HSR to P [3, 4].

The occurrence of an anaphylactic shock in our hospital, in a patient with a history of S-HSR to D who crossed over to P, prompted us to assess the possible risks by determining the proportion of cross-reactivity between P and D among patients who received both drugs.

Patients and methods

Data were collected retrospectively using CHIMIO software, which manages drug prescriptions between 1 January 2007 and 31 December 2010.

Initially, we extracted patients treated with D or P, all diseases combined. We crossed these data to determine the number of patients who were treated with both chemotherapeutic agents. We were able to identify patients who received D following treatment with P and those who received P following treatment with D.

In a second step, using internal electronic medical records, we identified patients who presented with an HSR during their chemotherapy treatment. We collected data on: the age of the patient; the primary cancer; the treatment that the patient was on at the time of the HSR; the symptoms of the reaction; the time of occurrence and rank; whether therapy was discontinued as a result of the HSR which could explain the replacement of one taxane with another; the time between both taxanes; and additional examinations. Each S-HSR was notified to the regional pharmacovigilance centre.

Results

Between 2007 and 2010, 694 patients were treated with P and 1,401 patients with D. A total of 84 patients received both agents, see Figure 1. Patient characteristics are presented in Table 1. One patient was initially treated for breast cancer and a few years later for lung cancer.

Patients initially treated with P and subsequently with D

A total of 26 patients received first P and then D. Twelve of them (46%) presented with an HSR to P (respectively, eight and four during the first and second administration). For 10 of them, hypersensitivity was the only reason for switching to D. For two others, the occurrence of neuropathy and the discovery of a progression also prompted discontinuation of P. These 12 patients subsequently received D without an HSR. The other 14 patients did not experience any immediate HSR (neither with P nor D).

Patients initially treated with D and subsequently with P

A total of 58 patients received first D and then P. Twelve of them presented with an HSR to D (21%). All HSRs occurred during the first treatment and D was not reintroduced thereafter. For these 12 patients, hypersensitivity was the reason for switching to P. Seven patients received P directly after D. Of these, three presented with an immediate HSR including one S-HSR. A total of 46 patients had no HSR to D but, over the transition to P, two patients presented with an HSR eight days after the first administration.

Finally, our study reported a cross-reactivity rate of 12.5% if we consider the 24 patients who had an HSR with the first taxane (D or P) and of 3.6% when considering the 84 patients who received both agents. Table 2 summarizes these observations.

Discussion

Hypersensitivity reactions to D are characterized by severe hypotension, bronchospasm, and a generalized erythema. They can occur despite premedication with steroids.

Hypersensitivity reactions to P are characterized by hypotension, angioedema, respiratory distress, and generalized urticaria. Premedication includes steroids, and histamine receptor antagonists.

The occurrence of an HSR to taxanes may be a contraindication to their reintroduction. Nevertheless, a switch seems possible through standardized protocols for desensitization using

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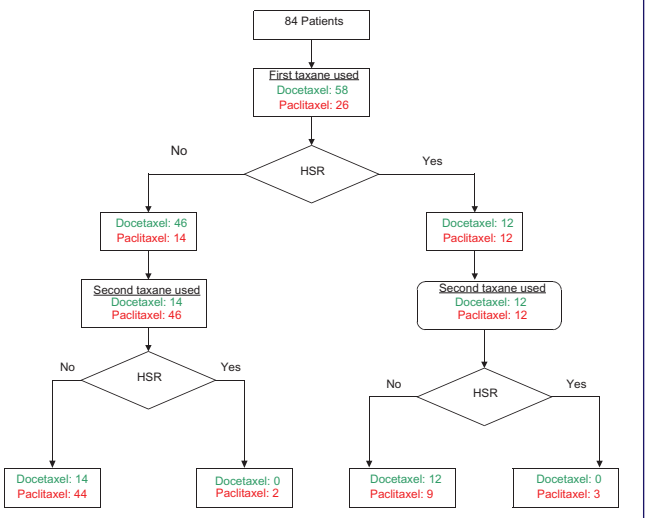
Figure 1: Hypersensitivity reactions with taxane treatment



HSR: hypersensitivity reactions

Table 1: Patient characteristics

Number of patients who received D and P	84
Age (average ± standard deviation, years)	57.6 ± 12.8
Gender (female/male)	77/7
Initial localization of the cancer - Ovary - Breast - Endometrium - Lung - Primary peritoneal carcinoma - Unknown	 9 (11%) 67 (80%) 1 (1%) 5 (6%) 1 (1%) 1 (1%)

dose levels, a gradual increase of the administration flow and of the concentration of D and P [5, 6].

If these protocols fail, the substitution of P by D is an alternative but the possibility of cross-reaction should not be underestimated.

Two retrospective studies described the occurrence of cross-reactivity in patients who were re-challenged with D after an HSR to P [3, 4]. The first study showed a rate of 90% of cross-reactivity [3]. However, the methodology was somewhat different from ours since in 16 patients who experienced an HSR to P, 10 were subsequently treated with D and nine patients experienced an S-HSR. The second study, whose methodology is similar, found a rate of 11% of cross-reactivity [4]. Using the same methodology, our study would yield a rate of 12.5% of cross-reactivity. These authors also provided recommendations regarding the use of D as an alternative to P: D may be used with caution in patients with a history of moderated HSR with P, whereas the use of D is contraindicated in patients who have had an S-HSR to P.

The exact etiology of taxane-induced HSRs has not been fully elucidated. Several hypotheses have been discussed, including: the role of excipients [7, 8]; the specific molecular structure of taxanes [9]; the release of vasoactive substances [8]; and neuropeptides [10] such as substance P and neurokin A, or nitric oxide [11]. However, the mechanism does not appear to be dependent on IgE [5], or related to the release of tryptase [8] or histamine [8-10].

The physicochemical characteristics of these two taxanes are problematic because structurally they have a low aqueous solubility not allowing an intravenous administration. Specific formulations have been developed: P is formulated with 50% ethanol and 50% Cremophor EL (Cr EL) and D is formulated with polysorbate 80 (Tween 80).

In vitro studies have highlighted the role of Cr EL in the activation of complement, contributing to the HSR to P [7].

Polysorbate 80 could not be the cause of the HSR with D because it has been approved for use in food products and is generally recognized as safe. It is also included in the composition of numerous medicines [8].

Most reactions to P and D were observed during the first injection, without prior sensitization to an antigen, involving a mechanism not dependent on IgE [5]. Our study supports this hypothesis.

On the other hand, the release of histamine seems controversial. A study conducted in rats showed no significant increase in histamine levels after injection of P [10]. Any involvement of histamine seems unlikely with either D or P, as HSRs occur despite premedication with histamine receptor antagonists. This suggests that mediators other than histamine are involved. Histamine receptor antagonist premedication is therefore questioned.

Tryptase, which is secreted during degranulation of activated mast cells, is an anaphylactic marker. Hypersensitivity reactions to D are not associated with the release of tryptase. In our study, the tryptase assay was performed in three patients who experienced hypersensitivity cross-reactivity, and tryptase levels were not elevated. Nevertheless, an allergic predisposition is a risk factor for developing HSRs [6].

Conclusion

Cross-reactivity between P and D is not rare and the substitution from one to the other with previous HSRs should be performed with caution. Clinicians should be aware of this risk.

Recently, cabazitaxel and nab-paclitaxel were added to the family of taxanes. Cabazitaxel is marketed and indicated for advanced prostate cancer in patients previously treated with D. Its activity is also evaluated in other indications such as metastatic breast cancer [12]. However, no bibliographic data supports the conclusion that cabazitaxel could be an interesting alternative when D and P are contraindicated. Nab-paclitaxel is paclitaxel encapsulated in albumin; this novel formulation of paclitaxel does not

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Table 2: Characteristics of cross-sensitivity with docetaxel and paclitaxel

Patient	1	2	3
Age (years)	43	53	39
Primary cancer	Breast	Breast	Breast
Number of D treatments leading to an allergic reaction	1	1	1
Symptoms of allergy to D	Oedema, erythema, chest tightness, dyspnea	Dyspnea, erythema, hypoxia, anaphylactic shock	Erythema, palpebral oedema
Time of onset	10 minutes	Immediate	Immediate
Grade (1 to 4)	2	3	1
Biological explorations	Normal tryptase and histamine	Normal tryptase and histamine	Tryptase and histamine not performed
Interval between D and P (weeks)	3	3	1
Symptoms of allergy to P	Erythema, dyspnea, chest tightness, malaise	Vomiting, mediastinal-thoracic pain, erythema, anaphylactic shock	Erythema, dyspnea, back pain
Time of onset	Immediate	Immediate	No data available
Grade (1 to 4)	2	3	2
Biological explorations	Normal histamine tryptase not performed	Normal histamine tryptase not performed	Tryptase and histamine not performed

require solvents, such as Cr EL and ethanol, which have been associated with a toxic response. Nab-paclitaxel is reported to improve tumour response and decrease hypersensitivity reactions in comparison with other taxanes for the treatment of metastatic breast cancer [13]. However, it is not yet clear whether nab-paclitaxel can be routinely substituted for Cr EL-paclitaxel or docetaxel in breast cancer treatment regimens.

Conflict of interest

All authors have no conflicts of interest.

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ASCO 2013: drug shortages critical for the treatment of common and curable cancers in the US

At the 2013 ASCO Annual Meeting in Chicago, USA, drug shortages were a key issue. Cancer drug shortages will likely be a persistent problem, forcing oncologists to switch treatment regimens, substitute alternate drugs part way through therapy, delay treatment, omit and reduce doses and to choose among patients.

Shortages of chemotherapy agents used to cure cancer patients

The increasing worldwide demand for generic oncology drugs coincides unluckily with short supply of raw materials, production problems (such as contamination of materials, ageing production plants, deficiencies in good manufacturing practice), reduced productive capacity because of limited profit margins for generic drugs and administrative over-regulation, resulting in gray markets, stockpiling, price gouging and drug shortages. In the long run, this will promote an increasing use of costly, not sufficiently established innovative treatments instead of well-tried generic drugs.

Professor Dr med Günther J Wiedemann, MD, PhD

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To prevent drug shortages, the early notification programme of the US Food and Drug Administration (FDA) has been implemented. This included establishing register of essential chemotherapy drugs, predictive analytical methods to detect potential drug shortages and identifying the patients most likely to be adversely affected by them [1-3]. Are there any effects of these efforts? Two surveys presented at the 2013 ASCO meeting give information.

Cancer drug shortages were common in 2012 and affected patient care. Cancer drug shortages will likely be a persistent issue

The 2013 ASCO survey shows that 59% of American oncologists and haematologists surveyed are aware of ongoing drug shortages in the community versus 70% in October 2012. Of all physicians surveyed, 17% said shortages were worse than in autumn 2012, 16% said they were the same, and 9% said that some shortages improved, but others, such as supportive care drugs, became worse. 46% of physicians surveyed are aware of the substitution of different treatment regimens in their community in the event of shortage, versus 60% in 2012.

Cost of care was driven upward, as physicians were forced to substitute cheaper generics with more expensive drugs

When oncologists are forced to switch from standard regimens, they often have to substitute a more expensive drug for the one in short supply, adding to patient anxiety and the costs of care, and potentially resulting in inferior patient outcomes.

Consequences of substituting cyclophosphamide for mechlorethamine in management of paediatric Hodgkin lymphoma

Mechlorethamine is used in the 12-week Stanford V chemotherapy regimen (an evolution of MOPP—Mustargen, Oncovin, Procarbazine, Prednisone) for treating Hodgkin lymphoma; the regimen usually includes vinblastine, doxorubicin, vincristine, bleomycin, etoposide, and prednisone. However, when mechlorethamine went into shortage in 2009, paediatric haematologists were forced to substitute with cyclophosphamide. A retrospective analysis of studies of children and adolescents with intermediate- and unfavourable risk Hodgkin lymphoma by the Pediatric Hodgkin Lymphoma Consortium compared the likelihood of event-free survival among 181 patients who were treated with the original regimen, including mechlorethamine, with 40 patients treated with the modified regimen, including cyclophosphamide. The study found that 88% of patients treated with the established regimen with mechlorethamine were expected to be event-free survivors at two years, compared to only 75% of those treated with the cyclophopshamide-containing regimen. Progress in cancer management in the past 50 years is thus hindered by shortages of relatively inexpensive, mostly older drugs that have been in use from the early days of oncology.

A second survey of 250 US oncologists and haematologists finds that more than 80% of the surveyed physicians encountered cancer drug shortages between March and September of 2012 and many reported that shortages affected the quality of patient care that oncologists and haematologists were able to provide (Gogineni Keerthi et al., Abrahamson Cancer Center, Department of Medical Ethics and Health Policy, Department of Health Care Management, University of Pennsylvania, USA).

Survey data show that cancer drug shortages persist and oncologists adapt in different ways

The surveyed oncologists reported that they were often forced to use more expensive brand name drugs instead of the standard generic and had to delay or modify treatment. Shortages have also interfered with patient participation in clinical trials, slowing the pace of research progress. Oncologists are adapting to

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this new reality as good as they can, but more uniform guidance is needed to ensure that modifications are made in the most educated and ethical way.

Drugs that are in short supply

- Folinic acid (66%)
- 5FU (62%)
- Liposomal doxorubicin (19%)
- Bleomycin (17%)
- Cytarabine (16%)
- Methotrexate (15%)

Cytarabine is particularly critical for curing certain forms of acute leukaemia.

When asked about the impact of cancer drug shortages over the prior six months, 94% reported that their patients´ treatment was affected and 83% were unable to provide standard chemotherapy. About 13% of respondents reported that shortages prevented patient enrolment or suspended participation in clinical trials.

How oncologists adapt to the shortage

- Switching treatment regimens (78%)
- Substitute alternate drugs part way through therapy (77%)
- Delaying treatment (43%)
- Choosing among patients to determine which one should receive the available supply of the chemotherapeutic agent (37%)
- Omitting doses (29%)
- Reducing doses (20%)
- Referring patients to another practice where drugs in shortage were available (17%)

Most providers (70%) said they had no international guidance committee to help make the difficult treatment modification decisions.

Conclusion

- The vast majority of practicing oncologists and haematologists face shortages of chemotherapy agents used to cure patients with cancer.
- Shortages forced providers to modify preferred treatment regimens.
- Shortages raise the cost of care.
- The majority had no guidance to aid decision making in the face of cancer drug shortages.

Standard treatment changing news and clinically meaningful outcomes

Breast cancer

Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at five years in women with early breast cancer

The objectives of this study were: firstly, randomize at least 20,000 women between five and 10 years of tamoxifen, to detect a 2–3% improvement in survival, and secondly, a follow-up of randomized women for at least 15 years (because in breast cancer trials 10 or more years are needed to see full benefits from a longer therapy with tamoxifen). **Continuing tamoxifen beyond five years reduces recurrence over the following years: no effects in years 5–6, benefit mainly after year 7. Continuing tamoxifen beyond five years also reduces breast cancer mortality: no effect in years 5–9, 24% reduction after year 10.**
(Gray R et al., University of Birmingham, UK)

Comparison of two schedules of paclitaxel as adjuvant therapy: weekly paclitaxel is less toxic for most patients

The schedules: Paclitaxel 175 mg/m² + Peg-filgrastim q2 wks x 6 versus Paclitaxel 80 mg/m², weekly x 12, combined with doxorubicin and cyclophosphamide. Rationale: Anthracyclines and taxanes are components of most modern chemotherapy regimens. Adding new chemotherapy drugs has not helped. We need to give the active drugs in the best way.

Results: Relapse-free survival produced by 6 cycles of q2 week paclitaxel and 12 weeks of weekly paclitaxel are similar. Low blood counts were observed more commonly with weekly paclitaxel, but these patients had blood counts checked more often and did not receive blood growth factors. Allergic-type reactions, aching, and nerve pain were more common in patients treated q2 weeks.
(SWOG [Southwest Oncology Group] S0221; Budd GT et al.)

Radiotherapy or surgery of the axilla after a positive sentinel lymph node: radiotherapy to the axilla is a good alternative to surgical removal of the lymph nodes

Breast cancer can spread to lymph nodes in the axilla (sentinel node: first lymph node to which the breast cancer spreads). If the breast cancer has spread to the sentinel node and treatment is indicated, the current standard therapy is surgical removal of all axillary lymph nodes to prevent cancer recurrence in the axilla. The undesired effects of surgical removal of axillary lymph nodes are oedema of the arm, impairment of shoulder movement and decrease in quality of life. The hypothesis of the trial was, if radiotherapy to the axilla instead of surgery was given, the same rate of cancer recurrence in the axilla and less undesired treatment effects would be seen. **The trial shows an extremely low rate of cancer recurrence in the axilla in both treatment groups and less oedema of the arm after radiotherapy.**
(EORTC [European Organization for Research and Treatment of Cancer] AMAROS; Rutgers EJT et al.)

Thyroid cancer

Sorafenib is a potential new treatment for patients with radioactive iodine-refractory differentiated thyroid cancer

In approximately 5–15% of patients with differentiated thyroid cancer, the disease becomes refractory to radioactive iodine treatment. No standard therapy exists for patients with disease progression. In an international, multicentre, randomized, double-blind, phase-III trial (417 patients) of sorafenib (400 mg

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orally twice daily) versus placebo, it was demonstrated that sorafenib significantly improved progression-free survival by 5 months compared with placebo. Sorafenib reduced tumour size in most patients. Toxicity results were consistent with the known toxicity profile of sorafenib.
(Brose MS et al., University of Pennsylvania, PA, USA)

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Feature

Biosimilars in oncology: current and future perspectives

Matti Aapro, MD

Cancer represents a significant, and growing, burden on healthcare systems by escalating cancer drug budgets. Available evidence indicates that biosimilars approved by regulatory authorities offer a safe and effective alternative to originator biological therapies. Therefore, greater adoption of biosimilars represents a key approach to reducing healthcare expenditure and improving patient access to important treatments.

The healthcare burden of cancer

Cancer places a significant, and growing, burden on healthcare systems around the world. Improved therapies and changing demographics are conspiring to increase the already considerable drain on resources. On the one hand, population growth and ageing will increase the number of new cancer cases in the coming years [1]; on the other, advances in diagnosis and management will extend the length of treatment required for each patient [2]. Many novel treatments or supportive therapies for patients with cancer are biological agents. In fact, cancer is the major indication for six of the ten best-selling biological therapies [3]. The cost of new cancer drugs is rising every year [4], due in part to the higher research and development costs associated with biological rather than chemical medicines. In the US, the cost of cancer drugs rose four-fold between 1998 and 2008 [5], with more than 90% of the oncology therapies approved by FDA between 2005 and 2009 costing in excess of US$20,000 for three months of treatment [6]. This growing cost burden is also being felt across Europe. The French budget for cancer therapies, for example, more than doubled from Euros 474 million to Euros 975 million between 2004 and 2008 [7]. These different factors form a complex situation that requires rapid action [8, 9].

Patent expiration on biopharmaceutical products provides pharmaceutical companies with an opportunity to develop and produce similar biological medicinal products, or biosimilars [10]. These agents may offer one way of controlling cancer drug expenditure while simultaneously expanding patient access to important treatments [11]. This article will review current and future use of biosimilars in oncology, regulatory aspects of biosimilar approval, and current and future impact of these agents on cancer drug expenditure.

Biosimilars in oncology: regulatory considerations

Biological therapies are large, highly complex molecules derived from living cells or organisms. Traditional chemical medicines, by contrast, are usually simple molecules of low molecular weight, synthesised by chemical means. These differing complexities and methods of manufacture create an important difference between biosimilars and conventional generic drugs: while chemical generics can be fully characterised as identical to the originator product, biosimilars cannot. Biological systems are inherently variable, creating unavoidable differences between even subsequent batches of the same product [12]. An expiring patent does not necessarily provide access to the precise manufacturing conditions used in producing the originator therapy, including, for example, the relevant cell line clone and growth medium. It therefore cannot be guaranteed that biosimilar products are identical to their reference product on a molecular level. In turn, this difference has

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important implications for the regulation and licensing of biosimilars. While conventional generic drugs require only a limited comparison and demonstration of identity to the reference product, biosimilars require far more rigorous testing. In general, there must be a thorough comparison of structural and functional characteristics of the biosimilar and originator therapy. Any identified microheterogeneities must then be assessed for their impact on safety and clinical performance.

In the EU, biosimilars are licensed through a thorough comparability exercise with the reference product, and clinical studies to ensure equivalence of efficacy and safety profiles. Guidelines produced by EMA detail manufacturing process requirements, and the range of protein structure, isoform, aggregate, receptor binding and biological activity assays necessary to demonstrate biological equivalence [13]. EMA guidelines also outline the required clinical and non-clinical pharmacokinetic, pharmacodynamic and pharmaco-toxological evaluations necessary to assess safety and efficacy before approval [14, 15]. EMA guidelines have served as a starting point for development of licensing procedures in the US, where FDA released draft guidance for the regulatory review of biosimilars in early 2012 [16].

A number of biopharmaceutical agents will lose patent protection in Europe from 2014 onwards, and as a result more biosimilar medicines are likely to become available for use in oncology [17]. The focus of biosimilar development will shift from medicines used in the supportive care setting to agents that provide life-saving or life-extending benefits such as monoclonal antibodies (mAbs). Following an extensive public consultation period, EMA has recently adopted its guideline on biosimilar monoclonal antibodies [18]. It recognises the challenges that manufacturers may face in establishing similar clinical efficacy and safety of a biosimilar and reference mAb in the anticancer setting; preferred endpoints for confirming efficacy, such as progression-free, disease-free and overall survival, may not be feasible to establish biosimilarity as they may be influenced by factors, e.g. tumour burden, performance status, previous therapy, unrelated to differences between the biosimilar and reference mAb. The guideline therefore acknowledges that surrogate endpoints such as overall response rate or change in tumour mass may be more appropriate.

Biosimilars in oncology

All biosimilar medicines currently approved by EMA are versions of recombinant human erythropoietin (epoetin), recombinant human granulocyte colony-stimulating factor (filgrastim) or recombinant human growth hormone. The biosimilar epoetins and filgrastims are used in oncology, for the treatment of chemotherapy-induced anaemia (biosimilar epoetins) and prevention of chemotherapy-induced neutropenia (biosimilar filgrastims). The availability of biosimilars has generated discussion among physicians about the possible concerns with prescribing these products [19].

The primary safety concern for biosimilars, as for all biological medicines, is immunogenicity. Most biological therapies elicit an immune response, in most cases with no clinical consequences. However, there are some biologicals for which immune responses have been linked to serious safety issues, notably the pure red-cell aplasia (PRCA) caused by cross-reacting neutralising antibodies against erythropoietin. Even small structural alterations may have an impact on immunogenicity, and analytical or animal data cannot always predict human immune responses. To mitigate this unavoidable risk, extensive non-clinical trial data demonstrating no increase in immunogenicity of the biosimilar compared with the reference product are required before a biosimilar can be licensed. In fact, the risk for detection of new and serious adverse effects after licensing is considered by some to be much lower for a biosimilar than for a biological containing a new or modified active substance [20]. Furthermore, the newer technologies used in manufacturing biosimilars mean that the products are generally of higher purity and quality, and more consistent potency, than their originator reference products [21]. Unfortunately, inadequately produced copies exist and can lead to major issues, as recently exemplified by numerous cases of PRCA in Thailand [22].

Ongoing pharmacovigilance is key to ensuring the safety of biopharmaceuticals. The pharmacovigilance programmes put in place by companies who market biosimilars are comparable in size and scope to those of originator companies, including a requirement to provide periodic safety update reports to the regulatory authorities. EMA requires a risk-management plan (RMP) to be implemented as a condition of marketing approval for all biopharmaceuticals, whether originator or biosimilar products. As an example, biosimilar epoetins have post-marketing studies as part of their RMPs to address potential safety issues such as PRCA, thromboembolic events and tumour treatment outcomes.

Patient exposure to biosimilars is increasing as adoption of these agents becomes more widespread. For example, the current (as of March 2013) estimated exposure to Binocrit (a biosimilar epoetin alpha) is over 200,000 patient-years, with more than 5,000 patients studied in clinical trials (data from the Sandoz periodic safety update report to EMA). As another example, the current estimated exposure to Zarzio (a biosimilar filgrastim) is 3.5 million patient-days. It is reassuring that the adoption of biosimilars in general has so far not been associated with any unexpected safety concerns. A recent review of information gathered since biosimilar epoetins entered the market identified no difference in safety profiles between biosimilar and reference products, or between the alternative biosimilar formulations [23]. Similarly, a prospective randomised clinical study, conducted since licensing, has shown equivalence in pharmacokinetic and pharmacodynamics profiles, safety and clinical efficacy between originator and biosimilar epoetins [24].

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Cost savings associated with biosimilars: current evidence and future possibilities

Available evidence indicates that biosimilars offer a safe and effective alternative to originator biological therapies. They also offer potentially significant cost savings to healthcare authorities, which are desperately needed to control the current unsustainable levels of expenditure; sales of biopharmaceuticals amount to almost US$70 billion in the US and Euros 60 billion in Europe [3, 25]. The development, manufacture and licensing requirements for biosimilars are considerably more rigorous than those for traditional generic drugs. The cost savings are therefore unlikely to be as large as sometimes observed for conventional generics, with savings in the region of 15–30% rather than 80% [26, 27]. A recent quantitative analysis of the European biosimilar market also concluded that biosimilars will result in smaller price reductions (and smaller market share) than conventional generic medicines [28]. Nevertheless, the potential cost savings are substantial – by some estimates, a 20% reduction in the price of six off-patent biopharmaceuticals would save Euros 1.6 billion in Europe each year [29].

There is already evidence of the cost savings being made through adoption of biosimilars. For example, it is estimated that biosimilar epoetins saved Euros 60 million in Germany during their first year of availability – a figure that is projected to rise to Euros 8 billion by 2020 (IGES 2010). Another analysis across seven European countries (France, Germany, Italy, Romania, Spain, The Netherlands and UK) calculated 2010 expenditure on epoetins in oncology to be US$1,117 million [17]; assuming a 100% switch to a biosimilar epoetin (at 2010 prices), US$188 million would be saved per annum. A recent study has attempted to systematically forecast the savings that could be made by increasing use of biosimilar epoetin, filgrastim and monoclonal antibodies in eight European countries – France, Germany, Italy, Poland, Romania, Spain, Sweden and UK [30]. Analysis was based on prices between 2007 and 2010, and an estimate of future drug consumption through either theoretical requirements based on demographic and epidemiological estimates, or through estimated growth rates. A range of country-specific scenarios were developed for the market and price progression of each biosimilar and its originator product. Assuming no biosimilars entered the market, estimated expenditure on the investigated biological therapies was Euros 229 billion between 2007 and 2020. By 2020, savings from biosimilar use ranged from Euros 11.8 to Euros 33.4 billion, depending on the model used. This represents 5.2% to 14.6% of total therapy expenditure. The bulk of these savings are expected to be made in France, Germany and UK – the countries that currently spend the most on biological drugs. Projections are likely to be most accurate for biosimilar epoetins, since these have been available in Europe for several years and therefore have known market trends. Here, savings of between Euros 9.4 and Euros 11.1 billion are estimated up to 2020 – a reduction of 21.5–25.5% from the baseline originator-only scenario. A model specifically designed to compare the comparative cost-efficiency of originator and biosimilar epoetins found that, for a patient undergoing six cycles of chemotherapy, the average cost of treatment was reduced from Euros 7,168 to Euros 4,643 through the use of biosimilar rather than originator epoetin alpha therapy [31].

Biosimilars in oncology: how can they improve patient care?

The potential cost savings through adoption of biosimilar medicines are important to society in general, but it is also important to consider how adoption of these agents might improve patient care. One possibility is that improved affordability may increase patient access to the most appropriate therapies at an earlier time during their illness. In a non-interventional study conducted in a community oncology centre, switching from originator to biosimilar filgrastim was accompanied by a trend towards increased use of filgrastim as primary prophylaxis [32], which may reflect greater willingness to use biosimilar filgrastim earlier given its lower cost. Another possibility is that cost savings made by using biosimilar medicines in the supportive care setting could be re-invested to expand patient access to currently available life-extending or life-saving treatments. As an example, the saving of US$188 million generated by switching to biosimilar epoetin (described previously) would support rituximab therapy for an additional 9,000 patients [17]. Finally, with upwards of 500 oncology biologicals currently in development pipelines, a third possibility is that greater uptake of existing and future biosimilars will permit funding of these new biological cancer treatments.

Conclusion

In the current climate of growing financial constraints on healthcare systems and impending patent expiry on major biological therapies used in oncology, biosimilars offer an important opportunity to provide high quality and clinically effective medications at reduced cost. Their greater affordability may, in fact, result in clinical benefits through earlier and wider therapy use, and release of funding to be used elsewhere in clinical care. With the appropriate regulation and monitoring in place, increasing adoption of biosimilars represents a key approach in reducing healthcare budgets and improving patient access to important therapies.

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