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Oral medication for cancer patients – the hour of pharmacy has come

Klaus Meier
Editor-in-Chief
EJOP

In June 2014, more than 500 pharmacists from 40 different countries gathered together in Krakow, Poland, at the 2nd European Conference of Oncology Pharmacy (ECOP) [1], to share scientific developments.

One of the aims of the European Society of Oncology Pharmacy (ESOP) is to promote the pharmacist as an important and recognized member of the multi-professional community in order to provide cancer patients with the best possible treatment. The word 'cancer' still stigmatizes people throughout the world and it is still strongly linked in people's minds with death. In fact, cancer will soon be declared the main cause of death worldwide. This may be because people are living longer and that 66% of all cancer patients are over the age of 65 years.

The standard of living in developed and developing countries is improving, and life expectancy is increasing. The development of new forms of cancer treatment has transformed cancer from a fatal illness into a chronic one. This increases the importance of the pharmacist in providing holistic pharmaceutical and medical care.

Nevertheless, we need to recognize that the political landscape has changed and that we are experiencing many contradictions. Borders established through peace treaties are no longer recognized. Conflicting interests are colliding with one another. Doctors preach: 'do not harm' – that is also our aim. We only have one world and we need to protect it.

Therefore, we as pharmacists must emphatically promote our profession. The important role of the pharmacy was also recognized by the Commissioner for Health and Consumer Policy Tonio Borg, as he accepted the patronage of the ECOP 2 (2014) in Krakow, Poland.

Will European political leaders recognize and use pharmacists to help prevent and treat cancer? And will pharmacists also be able to hurdle economic obstacles to present their achievements in the light of their skills?

Studies have shown that increasing duration of regular tablet use decreases adherence. A study published at the last ASCO (Abstract 11562), however, showed the opposite. A total of 150 patients with diverse cancers taking an oral anticancer drug (oral targeted agent or oral chemotherapy agent) were observed prospectively. At each cycle of oral treatment, an oncology pharmacist counted the tablets taken and any remaining tablets. Compliance and adverse events were recorded. Almost all patients were compliant (91%). Patient preferences were surprising. In patients who had serious adverse events, almost all (95.6%) did not stop their oral treatment when major toxicity occurred.

The authors found that a major potential risk for patients can occur if patients do not seek the advice of a qualified pharmacist. The patients who did not stop oral anticancer treatment even when major toxicity occurred believed that these were side effects of the therapy that needed to be endured. It is these patients who need professional support and education.

The provision of information and pharmaceutical care for cancer patients is an indispensable good that pharmacists can provide and should not be taken away from them. All pharmacists should be helped to enhance their knowledge and prepare for rising demand.

ESOP is applying for recognition at the European Commission. Let us hope that the European community has had sufficient time to learn about our strengths.

Reference

1. 26–28 June 2014, ECOP 2 in Krakow, Poland, organized by the European Society of Oncology Pharmacy (ESOP).

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.

Tyrosine kinase inhibitors becoming generic drugs – risks and chances from a regulatory perspective

Niels Eckstein, PhD; Lea Röper, BSc; Bodo Haas, PhD; Henrike Potthast, PhD; Ulrike Hermes, PhD; Christoph Unkrig, MD; Frauke Naumann-Winter, PhD; Harald Enzmann, MD

Abstract

Aim: To provide a systematic overview on: i) safety profiles; ii) pharmacokinetic parameters; and iii) regulatory framework of anti-cancer tyrosine kinase inhibitors (TKI).

Methods: Search of pharmakokinetic (PK)-parameter: i) Germany's federal drug database (public domain part) was accessed in November 2013. Section 5.2 (PK) of Summary of Product Characteristics systematically was searched for available PK-parameters; and ii) A search in PubMed/Medline was performed also in November 2013 using the international non-proprietary name of the respective medicinal product combined with the term 'early phase' or 'dose escalation'. PubMed search was restricted by searching only in clinical trials.

Safety profile assessment: On 11 November 2013, Summary of Product Characteristics of currently marketed medicinal products was accessed. Side effects were categorized as mentioned in the table's legend by frequency for each preferred term of the systems organ class system. Source: Summary of Product Characteristics published on the Heads of Medicines Agencies homepage: http://mri.medagencies.org/Human

Results: PK-parameters and safety profiles are presented in the respective tables. Throughout the text, clinical meaning, orphan drug status and current discussion on narrow therapeutic index (NTID)-status by European committees and working parties is discussed.

Conclusion: Tyrosine kinase inhibitors are a valuable addition of the therapeutic armamentarium. Especially in certain haematologic diseases, i.e. chronic myeloid leukaemia (CML)-therapy, TKI have revolutionized pharmacotherapy with survival rates not significantly different from healthy matched population. However, as their safety profile differs substantially from conventional cytostatic drugs, new side effects impact on patient's quality of life. About 10 years after first substances were authorized, patent protection will end within the next years. Thus, product specific guidance is needed to accurately perform bioequivalence studies and file marketing authorization applications for registration of TKI-generics.

Keywords: Generics, narrow therapeutic index drugs (NTDI), orphan drug status, Product-Specific Bioequivalence Guidance, tyrosine kinase inhibitors (TKI)

Introduction

Initially, great expectations were associated with these drugs; some were met, others not. Tyrosine kinase inhibitors (TKIs) are a very worthy additional option for physicians in clinical management of certain types and lines of treatment of cancer, see Table 1 for a tabular overview. In haemato-oncology, they are contributing to the tendency of chronificating rather than curing the disease. In contrast, the expectation of a new era of cancer-therapy without or at least substantially less side effects were not fulfilled, TKI have numerous, partly severe side effects eventually entailed with fatal outcome, see Table 2. On the other hand, after evolving of resistance to conventional (cytotoxic) or targeted anti-cancer therapy, TKI serve as additional therapy options in second, third and/or fourth-line therapy regimes according to their approved indications. For instance, Sunitinib is approved after Imatinib resistance formation in gastrointestinal stromal tumours (GIST), and Lapatinib after non-responding to antracycline- or taxane-based chemotherapy in combination with Trastuzumab in HER-2 positive breast cancer. Taken together, TKI are a valuable extension of the cancer drug armamentarium [1, 2].

Challenges of generic TKI drugs in cancer therapy

According to their European birth date during the past decade, these substances successively will be running off-patent within the next years, see Table 1. From a regulatory point of view, this raises the question how marketing authorization applications (MAA) should be filed and especially, how therapeutic equivalence should be established for generic applications. In general, demonstrated bioequivalence (BE) allows generic medicinal products to refer to the efficacy and safety data of the originator medicinal product. It is easy to anticipate, that numerous questions in this regard will arise in the near future.

Aqueous (non-complicated) intravenously applied drug products have a 100% bioavailability directly per definition, thus, no BE studies are required for a MAA of such generic drugs. However, for orally applied drug products, BE with the originator product needs to be shown, which may be done using patients or healthy volunteers in respective *in vivo* studies or by means of comparative *in vitro* investigations.

Since decades BE-acceptance criteria for area under the curve (AUC) and, maximum plasma concentration (C_{max}) require the

Table 1: General information on anti-cancer tyrosine kinase inhibitor (TKI)

TKI (INN)	Branded name	Market authorization holder (MAH)	Target tyrosine kinases	Indication(s)	European birth date	CMA[3]	Orphan designation
Bosutinib	Bosulif	Pfizer	BCR-ABL, SRC	Patients with CML for which Imatinib, Nilotinib, and Dasatinib are not appropriate	27 March 2013	Yes	CML
Dasatinib	Sprycel	Bristol-Myers Squibb	BCR-ABL	CML	23 December 2005	No	CML, ALL
Erlotinib	Tarceva	F. Hoffman-La Roche	EGFR	NSCLC, pancreatic cancer	19 September 2005	No	No
Gefitinib	Iressa	AstraZeneca	EGFR	NSCLC in carriers of activating EGFR-mutations	24 June 2010	No	No
Imatinib	Glivec	Novartis	BCR-ABL, KIT, PDGFR-A, PDGFR-B	CML, GIST, BCR-ABL-positive ALL, dermatofibrosarcoma protuberans, myeloproliferative neoplasms, hypereosinophilic syndromes	7 November 2001	No	Expired and withdrawn
Lapatinib	Tyverb	GlaxoSmithKline	ERBB2 (HER-2)	HER-2 positive breast cancer	10 June 2008	Yes	No
Nilotinib[1]	Tasigna	Novartis	BCR-ABL, KIT, PDGFR-A, PDGFR-B	CML	19 November 2007	No	CML
Pazopanib	Votrient	GlaxoSmithKline	VEGFR, PDGFR, KIT	Renal cell carcinoma, STS	14 June 2010	No	Withdrawn
Ponatinib[2]	Iclusig	Ariad	BCR-ABL	Patients with CML for which Imatinib, Nilotinib, and Dasatinib are not appropriate (or patients carrying a T315I single-point-mutation)	1 July 2013		CML, ALL
Sorafenib	Nexavar	Bayer	VEGFR-2, VEGFR-3	Renal cell carcinoma, hepatocellular carcinoma	19 July 2006	No	Renal cell carcinoma, hepatocellular carcinoma
Sunitinib	Sutent	Pfizer	VEGFR 1–3, PDGFR-A, PDGFR-B, KIT, FLT3	Renal cell carcinoma, GIST, pNET	19 July 2006	Initially, then full approval	Withdrawn

ALL: acute lymphatic leukaemia; CML: chronic myeloid leukaemia; EGFR: epidermal growth factor receptor; GIST: gastrointestinal stromal tumour; INN: international non-proprietary name; NSCLC: non-small cell lung cancer; PDGFR: platelet-derived growth factor receptors; pNET: pancreatic neuroendocrine tumours; STS: soft tissue sarcoma; TKI: tyrosine kinase inhibitors.

[1]Nilotinib is similar to Imatinib according to the orphan regulation.

[2]US Food and Drug Administration asked the manufacturer of Ponatinib to suspend marketing due to the risk of life-threatening blood clots and severe narrowing of blood vessels.

[3]CMA: conditional marketing authorization (none of the above-mentioned is currently authorized under exceptional circumstances, according to European Medicines Agency website accessed in September 2013 [4]).

Source: European Public Assessment Reports (EPARs) of the above-mentioned TKI [4]

90% confidence intervals being completely within 80–125% (for AUC and C_{max}) to assume BE. The acceptance range may be tightened to 90–111% for one or both pharmacokinetic (PK) characteristics according to the European BE-Guideline [3] in the case of narrow therapeutic index drugs (NTID). In cases of class I and III compounds having identified not to have a narrow therapeutic index – specific *in vitro* dissolution data may substitute for human BE-studies considering also particular requirements on excipients. This concept follows the principles of the biopharmaceutical classification system (BCS) [3].

It is likely that numerous questions in regard to the appropriate data package will arise in the near future including questions on the appropriate study design, on the appropriate study population, nutrition status, single or repeated dose design, appropriate BCS classification of the individual compound or the classification as NTID.

MAA for new generics may be processed via different regulatory authorizations routes, i.e. national procedures in European Member States, decentralized procedures involving several European Member States or centralized procedures for all European

Table 2: Safety profiles of tyrosine kinase inhibitor (TKI)

Small molecule TKI (INN)	CNS	Nerve disorders	Eye disorders	Heart disorders	Lung airways disorders	Thyroid disorders	Liver, bile disorders
Bosutinib		XX		XX	XX		XX
Dasatinib	X	XX	XX	XX	XX		X
Erlotinib	X	XX	XX		XX		X
Gefitinib			XX		XX		XX
Imatinib	X	XX	XX	X	XX	X	XX
Lapatinib	X	XX		X	XX		XX
Nilotinib	X	XX	XX	XX	XX		XX
Pazopanib		XX	XX	X	XX	XX	XX
Ponatinib		XX	XX	XX	XX		XX
Sorafenib	X	XX		X	X		X
Sunitinib	X	XX	XX	X	XX	XX	X
Small molecule TKI (INN)	**Gastrointestinal disorders**	**Renal disorders**	**Musculoskeletal and bone disorders**	**Blood and lymphatic system**	**Vascular disorders**	**Skin disorders**	**CMR**
Bosutinib	XX	XX	XX	XX		XX	
Dasatinib	XX	X	X	XX	XX	XX	XX
Erlotinib	XX	XX		X		XX	XX
Gefitinib	XX	XX			XX	XX	XX
Imatinib	XX	X	XX	XX	X	XX	XX
Lapatinib	XX		XX		XX	XX	XX
Nilotinib	X	X	X	XX	X	XX	XX
Pazopanib	XX	XX	XX	XX	XX	XX	XX
Ponatinib	XX		XX	XX	XX	XX	
Sorafenib	X	X	X	XX	XX	XX	XX
Sunitinib	XX	XX	XX	XX	XX	XX	XX

CMR: carcinogenic, mutagenic and toxic for reproductive system; CNS: central nervous system; TKI: tyrosine kinase inhibitors.
INN: International Nonproprietary Name; X = rare, uncommon; XX = common, very common.
Source: Summary of Product Characteristics (SmPCs) of marketed TKI [5]

Member States. As the latter is an option only for generics for which the originator medicinal products already obtained marketing authorization from a centralized procedure, this option may receive more attention with the increasing number of medicinal products with centralized authorizations that are running off data protection and patent in the next years.

With the intent to enable a consistent approach for these different routes the European Medicines Agency (EMA) issued an initiative to harmonize the data requirements throughout European Member States, i.e. EMA initiated a pro-active programme 'Product-Specific Bioequivalence – Guidance for Generics' [4]. EMA defines the objective of this initiative as follows: 'Product specific guidance for the bioequivalence assessment of immediate release generic formulations should *a priori* be defined.' Thus, applicants should be given a clear scientific guidance, how to design BE-studies and, thus, how to file generic applications. This programme includes BCS classifications for drug substances, so that a harmonized view on the BCS classification and consequently the appropriateness of a BCS-based biowaiver approach can be expected for respective products. Furthermore, the guidance provides information on the type of expected data, e.g. appropriate study population (patients or healthy volunteers), mode of administration (fasten or fed), single dose or steady-state design, appropriate dose strength and analytes, the classification as NTID. The first wave of 16 medicinal products is dominated by anti-infectives and TKI. Dasatinib, Erlotinib, Imatinib, Sorafenib and Sunitinib are covered in this first round of harmonization [4].

From a clinician's point of view regarding drug safety, see Table 2, one could be tempted to assume that all anti-cancer medicinal products including TKI are considered as NTID. However, this is not the case. Different definitions of NTID by different regulatory agencies do exist. US Food and Drug Administration classification of **narrow therapeutic ratio**:

- less than a 2-fold difference in median lethal dose (LD_{50}) and median effective dose values (ED_{50}), or

- less than 2-fold difference in the minimum toxic concentrations (MTC) and minimum effective concentrations (MEC) in the blood, or
- safe and effective use of the drug products requires careful titration and patient monitoring.

In contrast to the US, for the EU no list of substances with NTID-designation is available. So far the consideration of a given substance as NTID is mainly based on national traditions. Only for a few medicinal substances, e.g. Ciclosporine, Tacrolimus, a harmonized EU decision was issued by a referral procedure. According to the draft 'Product-Specific Bioequivalence - Guidance for Generics' no drug is newly considered as NTID, only Tacrolimus is considered as such based on the previously finalized referral procedure.

According to the European Bioequivalence Guideline [3] clinical considerations are the basis for NTID decisions. Thus, safety and efficacy profile have to be taken into account.

Most conventional cytotoxic medicinal products are given parenterally for a short duration in repeated cycles. They are mostly dosed on an individual basis, e.g. body surface or weight. The recommended dose is normally the maximum tolerated dose (MTD) or close to it.

Marketed TKI drugs are typically given continuously via the oral route and at a flat dose. Although a most effective and durable target saturation is the primary objective for dose development of TKI drugs, it is obvious that for several TKI drugs the recommended dose is the same as the reported MTD, e.g. Bosutinib, Pazopanib, Ponatinib or Sunitinib, see Table 3. The dose-limiting toxicities include grade 3 gastrointestinal and hepatic toxicities, grade 3 skin toxicities, grade 3 fatigue, and grade 3 hypertension. For Sunitinib grade 2 bullous skin toxicity, grade 3 fatigue, and grade 3 hypertension are reported as dose-limiting toxicities. Furthermore, at approximately twice the therapeutic concentration a grade 2 QT-prolongation is expected (Summary of Product Characteristics Sutent [5]).

From a clinical point of view there are arguments for consideration as an NTID for selective TKI which are elucidated for the example of Sunitinib: the dose of 50 mg/d is the recommended dose for renal cell carcinoma and the MTD at the same time. The documented adverse events (AE) and adverse drug reactions (ADR) are serious, and toxicity may be difficult to control due to long half-life of parent compound and main metabolite (40–60 h and 80–110 h, respectively). The described toxicity induces a high probability of dose reductions with the intent to reduce exposure. The patient safety may be impaired in case of an exchange between originator and generic medicinal product following dose reduction: dose reductions of 12.5 mg represent a 25% and 33% decrease from the recommended dose for renal cell carcinoma and neuroendocrine tumours of pancreatic origin, respectively. In case of exchange of the originator for a generic drug the AUC from the reduced dose of the generic may be nearly the same as the AUC from the normal dose of the originator if normal acceptance criteria for BE (90% CI for AUC and C_{max} 80–125%) are applied.

From a safety point of view it should be mentioned that chronic exposure to a dose that was identified as the maximum tolerable dose in a short-term study may render the tolerable short-term toxicity into intolerable long-term toxicity.

Safety of certain TKI

Dasatinib, Nilotinib and Bosutinib – CML (chronic myeloid leukaemia) – TKI with different safety profiles from a regulatory point of view and availability of second generation TKI

In general TKI are well tolerated in clinical practice, particularly, if compared with the toxicity of cytostatic drugs normally used in oncology. Often side effects are only mild (grade 2 and lower) and occur early in the treatment course. Frequently they last only some days or weeks and resolve spontaneously. Moreover, even if drug-related toxicity requires drug discontinuation, re-exposition is often successful and permanent dose reduction is rarely necessary.

The advent of Imatinib in 2001 has dramatically changed the prognosis in patients with CML: The five-year survival rate of patients with chronic phase CML improved from approximately 20% in the pre-TKI era to more than 90% [6]. In those patients who achieve a stable cytogenetic response with Imatinib overall survival is reported with 95.2% at eight years in the literature and thus does not differ statistically significantly from that of the general population [7]. Imatinib is still the most common TKI modality used as a front-line therapy in CML across the world. However, due to the occurrence of Imatinib resistance and intolerance, second generation TKI as Dasatinib, Nilotinib and Bosutinib have been developed. In non-clinical models they are 30 to 300 times more potent than Imatinib and can inhibit most Imatinib-resistant BCR-ABL mutations (EPARs for Imatinib, Dasatinib and Nilotinib [4]). Comparable with the experience in anti-infective drugs, multidrug-resistant BCR/ABL mutations occurs which preclude further use of the approved TKI. For example, patients with T315I mutation respond only on treatment with third generation TKI Ponatinib, which was specifically designed as a treatment option for these populations.

TKI indicated in CML have some side effects in common as myelosuppression, gastrointestinal complaints, rash, fatigue, headache and peripheral and periorbital oedema; however, intensity varies significantly between the different products. Other AE are peculiar of each drug: Imatinib has been uncommonly associated with severe heart failure, while Nilotinib is associated with QT prolongation, pancreatitis, increased rate of cardiovascular events, and occurrence of peripheral arterial occlusive disease (PAOD). Dasatinib may cause pleural, pericardial and peritoneal effusions; additionally interaction

Table 3: Clinical pharmakokinetic profiles of tyrosine kinase inhibitor (TKI) marketed in the EU

TKI	t_{max} (h)	Bioavailability (oral, %)	Concomitant food intake: effect on bioavailability	Concomitant food intake: FDA recommendation	V (L/kg) 70 kg subject assumed	Primary enzymes involved in metabolism	Major metabolites	Plasma half-life (h)	Plasma protein binding (%)	Suggested threshold for response or concentration attained in therapy (mg/L)
Bosutinib	6	18 [14] derived from colon tumour xenograft models		With food	131–214 [15]	CYP3A4	M2 (oxydechlorinated Bosutinib) M5 (N-desmethyl Bosutinib)		94–96	
Dasatinib	0.5–3	< 34	Increases AUC (14%)	With/without food	30–40	CYP3A4, FMO-3	M4 (BMS-582691), M5 (BMS-606181), M6 (BMS-573188)	3–5	92–97	0.01–0.1 [16]
Erlotinib	4	69–76	Increases bioavailability (24–31%)	Without food	3	CYP3A4, CYP3A5, CYP1A2	Norerlotinib (OSI-420)	41	92–95	> 0.5
Gefitinib	3–7	57	No effect	With/without food	24	CYP3A4, CYP2D6, CYP3A5 (possibly CYP1A1)	Norgefitinib (M523595)	48	79	> 0.2
Imatinib	2–4	98	No effect	With food	2–6 (Imatinib), 15–40 (Nor imatinib)	CYP3A4, CYP3A5, CYP2C8	Norimatinib (CGP74588)	12–20 (Imatinib), 40–74 (Nor imatinib)	95 (Imatinib and Nor imatinib)	> 1 (CML and GIST)
Lapatinib	3–5	–	Increases AUC (167–325%)	Without food	31	CYP3A4, CYP3A5	Norlapatinib (GW690006)	14	> 99	> 0.5 mean concentration in patients prescribed 1,500 mg once daily [17]
Nilotinib	3	30	Increases C_{max} (112%) and AUC (82%)	Without food	10–15	CYP3A4, CYP2C8	–	15–17	98	> 0.6 C_{min} concentration applicable to quartile 1 from cytogenetic response [18]
Pazopanib	2.8	14–39	Increases AUC and C_{max} (2-fold)	Without food	0.1–0.2	CYP3A4, CYP1A2, CYP2C8	Pazopanib M24, Pazopanib M26, Pazopanib M27	31	> 99	> 20
Ponatinib				With/without food		CYP3A4 (MRI PI)	inactive carboxylic acid		> 99	
Sorafenib	2–14	< 50	Reduces bioavailability (29%)	Without food	3–6	CYP3A4, UGT1A9	Norsorafenib, Sorafenib N-oxide (BAY 67 3472)	20–40	> 99	> 3
Sunitinib	6–12	–	No effect	With/without food	30	CYP3A4	Norsunitinib (SU12662)	40–60 (Sunitinib), 80–110 (Nor sunitinib)	95 (Sunitinib), 90 (Nor sunitinib)	> 0.05 (Sunitinib + Norsunitinib)

(*Continued*)

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Table 3: Clinical pharmakokinetic profiles of tyrosine kinase inhibitor (TKI) marketed in the EU (*Continued*)

TKI	DLT	MTD	Clinical dose (as recommended by SmPC)	Dosage form	Human AUC at the clinical dose (ng*h/mL)	*In vitro* IC_{50} values for target kinase inhibitor (ng/mL)	Dose-reduction	
							Liver	Renal
Bosutinib	Grade 3 diarrhea, grade 3 rash [19]	500 mg, q.d.	500 mg, q.d.	Tablet	2,740 ± 790	250 nM [20]		Decision pending
Dasatinib	Grade 3 nausea, grade 3 fatigue, grade 3 rash [21]	> 120 mg b.i.d	100 mg, q.d. (for chronic phase), 70 mg, b.i.d. (for accelerated phase and blast phase)	Tablet	398.8 (b.i.d. regimen)	0.0976	No, only in severe liver impairment	No
Erlotinib	Diarrhea [22]	150 mg, q.d.	150 mg, q.d.	Tablet	42,679	0.787 [23]	No	No
Gefitinib	Nausea, diarrhea, vomiting, rash	700 mg, q.d.	250 mg, q.d.	Tablet	7,251.5	12.1 [24]	No, only in severe liver impairment	No
Imatinib	Nausea, vomiting, fatigue, diarrhea	> 1,000 mg, b.i.d.	400 mg, q.d.	Tablet	33,200	12.3 [25]	Yes	No
Lapatinib	Rash, diarrhea, fatigue	1,800 mg, q.d.	1,250 mg, q.d.	Tablet	33,836.5	6.02 [26]	Yes	No, only in severe renal impairment
Nilotinib	Liver function abnormalities, thrombocytopenia [27]	600 mg, b.i.d.	400 mg, b.i.d. (for chronic-phase and accelerated-phase of chronic myelogenous leukaemia), 300 mg, b.i.d. (for newly diagnosed chronic-phase myelogenous leukaemia)	Capsule	19,000 (b.i.d. regimen)	not available	No	No
Pazopanib	Grade 3 aspartate aminotransferase (AST)/ alanine aminotransferase (ALT) elevations, grade 3 malaise [28]	800 mg, q.d. [29, 30]	800 mg, q.d.	Tablet	650 ± 500 µg*h/mL	10, 30, 47, 71, 84 or 74 nM	Yes	No
Ponatinib	Rash, fatigue	45 mg, q.d.	45 mg, q.d.	Tablet	77 (50 %) or 1,296 (48 %)	0.4 or 2.0 nM	Yes	No
Sorafenib	Hand-foot skin syndrome (HFS) [31]	600 mg, b.i.d.	400 mg, b.i.d.	Tablet	36,690 (b.i.d. regimen)	7.79 [32]	No	No
Sunitinib	Grade 3 fatigue, grade 3 hypertension, grade 2 bullous skin toxicity (HFS) [33]	50 mg, q.d.	50 mg, q.d.	Capsule	1,406	0.797	No, only in severe liver impairment	No

AUC: area under the curve; b.i.d.: twice daily; CML: chronic myeloid leukaemia; C_{max}: maximum plasma concentration; C_{min}: minimum plasma concentration; DLT: dose limiting toxicity; GIST: gastrointestinal stromal tumour; HFS: hand-foot syndrome; MTD: maximum tolerated dose; q.d.: every day; TKI: tyrosine kinase inhibitors; t_{max}: time after administration when C_{max} is reached.
Source: Summary of Product Characteristics (SmPCs) of marketed TKI [5] unless otherwise indicated

with platelet function is discussed to explain higher rates of gastrointestinal bleeding observed in clinical practice. Bosutinib is associated with significant gastrointestinal toxicity (diarrhea) and hepatotoxicity. Serious AE observed with Ponatinib are an alarming high rate of arterial thrombosis, and cardiovascular events as well as hepatotoxicity.

Differences in the safety profiles of these TKI seems to be at least partially explained by the additional inhibition of other signalling pathways apart BCR-ABL [c-Kit, Src family kinases, platelet-derived growth factor receptors (PDGFR), and others].

However, it should be kept in mind that TKI treatment of CML has to be administered lifelong and knowledge about potential long-term risks and efficacy, especially for the second generation TKI Dasatinib, Nilotinib and Bosutinib, is still limited. Whether risks associated with Ponatinib treatment can be tolerated is currently under discussion again.

Not only from a regulatory perspective careful attention on recommended risk minimization measures as defined in the product information is at the end essential to avoid treatment complications that may completely jeopardize the sought treatment success.

Can TKI be curative in CML? – Current strategies to avoid emergence of resistance

The availability of at least five TKI approved for the treatment for CML and the emergence of drug resistance and intolerance have induced a lively and complex debate on the best strategy to optimize TKI treatment.

Currently, CML treatment is ruled by the paradigm that patients with newly diagnosed CML who respond rapidly to initial treatment with a TKI and who do not develop severe intolerance against TKI should continue TKI therapy lifelong. On the other hand, long-term follow up of patients treated in the pivotal trials for Imatinib, Dasatinib and Nilotinib has shown that a relevant proportion of these patients not only achieved complete cytogenetic response but also sustaining reductions in BCR-ABL transcripts below the lower level of quantification ('complete molecular response'). Stability of BCR-ABL absence over years in these patients has led to speculations that these patients are cured of CML.

However, can treatment be discontinued safely in patients without evidence for minimal residual disease? Results from two studies (STIM; TWISTER) [8, 9] indicate that if TKI (Imatinib) is discontinued, more than half are expected to relapse within one year. At two years post-discontinuation, 47% of patients in TWISTER were still relapse free and remained off therapy. Those with molecular relapse responded to re-treatment, but patients may not attain the same degree of response upon re-treatment, which illustrates the potential risks of treatment discontinuation approach. As data available is derived from relatively small studies and follow-up is limited, larger studies are needed (and planned) to determine further the safety of such strategies. Thus, current CML treatment guidelines still recommend lifelong therapy with TKI.

Other open topics in the scientific discussions on TKI treatment in CML reflect the question, whether a more rapid and deeper molecular response observed for second generation TKI like Dasatinib and Nilotinib is clinically relevant and indicates a better prognosis. In this context high dose treatment (MTD approach) or sequential therapy with different TKI to lower development of resistance are under discussion.

The outstanding progress made in this area of therapy is best illustrated by the fact that since approval of Imatinib the 'gold standard' endpoint 'overall survival' is no longer sufficiently discriminative for clinical trials in patients with CML under TKI; surrogate marker as 'complete cytogenetic response' or 'major molecular response' have been validated and are now accepted as efficacy correlate by regulatory agencies.

Orphan drug status of TKI

The orphan regulation aims at fostering drug development for serious or life-threatening diseases with a prevalence of less than five in 10,000 people in the EU. A sponsor may apply for orphan designation any time prior to an application for marketing authorization (usually even before clinical development). The orphan drug status then needs to be confirmed during the marketing authorization procedure. The most important incentive of the regulation is 10-year market exclusivity for an orphan medicinal product with respect to similar medicinal products. Neither EMA nor EU Member States can authorize a product, which is regarded similar with respect to chemical structure and mode of action and therapeutic indication. Generics, by definition, fulfil all of these criteria.

Imatinib is the paradigm of targeted therapy with its target, the Philadelphia chromosome, occurring in two rare forms of cancer, CML and acute lymphatic leukaemia (ALL), which remain rare in spite of recent advances for treatment. Other cancers, e.g. renal cell carcinoma, was recently reported to exceed the prevalence threshold of five in 10,000 people so that no further orphan designations are expected.

Orphan similarity and market exclusivity

In addition to the incentive of the above-mentioned 10-year market exclusivity intended by the European orphan regulation [10], there may be a probably unintended additional incentive. Special circumstances are conceivable under which the market exclusivity granted for orphan products may exclude marketing authorization of a generic product. These special circumstances first occurred when the orphan drug Tasigna (Nilotinib) was assessed as 'similar' to Glivec (Imatinib). Glivec was first authorized in the EU in 2003. The Committee for Medicinal Products for Human Use (CHMP) gave a positive opinion on its benefit-risk balance, the Committee for Orphan Medicinal Products (COMP) confirmed the significant benefit and so

Glivec got the most important incentive for the development of medicines for orphan diseases – the market exclusivity. Under the condition of the European orphan drug regulation no medicinal product 'similar' to Glivec would get marketing authorization for 10 years – unless the similar product had superior efficacy or safety or the market authorization holder (MAH) of the protected product gives consent to the marketing of the similar product.

Several years after marketing authorization of Glivec was granted, similarity assessment of Tasigna concluded that Tasigna was a similar product to Glivec and the market exclusivity of Glivec would therefore be prohibitive for the authorization of Tasigna. In the context of a similarity assessment, three characteristics of a given drug are decisive:

1. the chemical structure (respectively structural similarity to the innovator product)
2. the molecular mechanism of action, and
3. the indication.

In the first step of Tasigna marketing authorization, this was not problematic, because Tasigna was first authorized in second line after first-line therapy with Glivec. However, with the extension of indications to first-line treatment of CML, Tasigna was authorized only with the consent of the MAH of Glivec (not surprisingly, as both medicines are products of Novartis). The COMP confirmed a significant benefit and thus Tasigna received its 10 years of market exclusivity beginning with the commission decision in 2007.

When data protection and orphan market exclusivity expired for Glivec generic Imatinib products to the reference product Glivec were submitted. There was, however, the previous regulatory decision that Glivec and Tasigna are similar products – including the assessment of Imatinib and Nilotinib as similar active substances based on their chemical structure and pharmacological mechanism. An authorization of a generic Imatinib product to the reference product Glivec would therefore not be granted if it violated the 10-year market exclusivity of Tasigna, which began in 2007.

It is safe to assume that the European orphan legislation was never meant to preclude the authorization of generics after the data protection and the 10 years orphan protection of the reference product had expired. And it also seems that this was not a deliberate abuse of a complicated legal and regulatory situation by Novartis but rather unintended. If that had been a wicked, albeit brilliant, marketing-driven strategy, the exact alignment of the indications of Glivec and Tasigna would have effectively prevented any Imatinib generics for many years. As the indications of Tasigna and Glivec overlap for the majority of patients but are not identical, a marketing authorization for Imatinib generics restricted to the indications not granted for Tasigna became possible. This is why the indications of generic Imatinib products are different from the indications of the reference product Glivec.

Is the approved dose recommendation always the right choice – notions on Erlotinib?

Sometimes the question is raised, whether dose-regimes for pivotal phase III studies (derived from early phases of clinical development) are the right ones. Especially with Erlotinib, where different dose regimes are recommended for different tumour types and toxicity is high, the question is raised: is there a *minimal effective dose* (MED) in epidermal growth factor receptor (*EGFR)-mutated tumours* below recommended dosage (or do patients indeed have to be titrated until MTD is reached)? In this regard, dose limiting toxicities (DLT) do not have to be the same for different tumour types or even in one tumour entity for all patients, see Table 3.

Regarding Erlotinib (apart from case reports) currently one publication is available, trying to bridge *in vitro* evidence directly with patient data [11]. This article is pointing to the fact that the MED of Erlotinib might in fact be below the recommended dose of 100 mg (pancreatic carcinoma) and 150 mg non-small cell lung cancer (NSCLC), respectively. The rationale of this study is: 'The usual clinical dose of Gefitinib (250 mg/day) is only one third of its MTD, while the dose of Erlotinib (150 mg/day) is at its MTD. In NSCLC cell lines both TKI have similar micromolar (µM) inhibitory concentrations.' Therefore, the authors investigated whether Erlotinib when administered at only 25 mg/day can inhibit the mutated form of the EGFR in NSCLC. Apart from similar *in vitro*-IC_{50}-values, blood concentrations of both drugs differ remarkably (by a factor of more than 5):

$C_{steady\ state}$ (Gefitinib at 250 mg/day) ~ 0.5 µM
$C_{steady\ state}$ (Erlotinib at 150 mg/day) ≥ 2.5 µM

These values were derived from early phase clinical development programmes of the respective drugs [12, 13].

The authors conclude: 'In NSCLC cell lines, Gefitinib and Erlotinib have similar inhibitory profiles. In patients with NSCLC and EGFR activating mutations, a dose of Erlotinib 25 mg/day (equivalent to Gefitinib 250 mg/day) leads to impressive response rates and progression-free survival similar to the growing experience with the approved doses of Gefitinib (250 mg/day) and Erlotinib (150 mg/day). Identifying prospectively the lowest, clinically active dose ranges of Erlotinib and Gefitinib will help further personalize care for patients with tumours harbouring EGFR mutations.' Unfortunately, this study is limited in evidence: it is basically an *in vitro* study correlated with data from only seven patients. Thus, no answer on what is the MED of Erlotinib can be given by now.

Conclusion

A decade ago, TKI were introduced into clinical anti-cancer therapy. At first sight, the molecular mechanism of action appears to comprise only a targeted approach in blocking tyrosine kinases. However, this should not be misleading; numerous closely interconnected signalling pathways are involved and the complexity of TKI molecular mechanism is far from being understood completely. For clinicians, TKI are a worthy new modality of tumour-therapy amending classical cytotoxic

regimes. TKI are of substantial benefit in terms of efficacy with a tolerable safety profile. However, long-term safety issues might not be fully elucidated at present and, thus, cannot be finally judged upon. Throughout the next years, many of these substances will run off-patent. Thus, regulatory guidance will be required for instance on whether certain substances like Sunitinib fulfil the criteria of a *narrow therapeutic index drug*. Apart from that, most TKI are orally administered, thereby raising the question whether BCS-based biowaiver can apply. In addition, design and requirements of BE-studies will be an issue in the EMA-initiative of product specific guidance on anti-cancer TKI.

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Disclaimer

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RESEARCH NEWS

Regulating the safety of biosimilars

Clinical safety is critically important during the development of a biosimilar. An overview of the main aspects of safety assessment of biosimilars has been prepared to assist all those interested in this area of growing importance [1].

In June 2013, the European Medicines Agency (EMA) released its 'Guideline for similar biological medicinal products containing biotechnology-derived proteins as active substances: non-clinical and clinical issues' for a six-month consultation [2]. The guideline, which forms the basis of this overview by Dr Thijs J Giezen of the Foundation Pharmacy for Hospitals in Haarlem, The Netherlands, and Dr Christian Schneider of the Danish Health and Medicines Authority, Denmark, lays down the non-clinical and clinical requirements for marketing authorization of a biosimilar claiming to be similar to a biological product already marketed.

The authors note that safety data should be collected throughout the complete clinical development programme of a biosimilar, and should be compared between the biosimilar and the reference product. Assessment of immunogenicity is especially important in this context due to the potential impact of changes in the production process and consequently on clinical safety. Differences in the safety profile will question biosimilarity and will require appropriate in-depth assessment and evaluation. Although differences in the safety profile are to be avoided, there is a possible exception when the biosimilar has a lower immunogenicity than the original reference product.

Extrapolation of safety data from one indication to the other is possible and should be justified, especially with regard to immunogenicity and potential differences in the characteristics of the patient population and the disease in which the biological is used.

The same rules and obligations apply for biosimilars as for any other biological, note the authors, which means that a Risk Management Plan (RMP) must be submitted as part of the application procedure as well as Periodic Safety Update Reports (PSURs) and the collection of adverse events identified and reported after approval.

Within the RMP, the knowledge obtained with the reference product should be the basis for the content of the RMP and the obligatory post-marketing requirements, including risk minimization measures.

Traceability is of paramount importance, conclude the authors, and all measures should be implemented to improve traceability.

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The role of the pharmacist in improving the safety of chemotherapy and treatment with monoclonal antibodies

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Abstract

Introduction: Chemotherapy and monoclonal antibodies are used increasingly to treat many diseases. These treatments continually evolve, calling on constant adaptation by healthcare workers. Despite what is known about the consequences of medication errors, and a growing safety culture, medication-related incidents are still detected by the pharmacist.

Study objective: This study assessed the pharmacist's role in improving healthcare quality and patient safety.

Methods: In collaboration with the patient safety team and the pharmacist, a medication error reporting system has been created in the hospital. According to the World Health Organization's (WHO) recommended taxonomy, the medication errors were reported by the pharmacists, physicians and nurses.

The retrospective data analysis of the treatment prepared and delivered by the pharmacy, during 24 months, concerned the chemotherapy, the monoclonal antibodies and concomitant/supportive therapies.

Results: Among the 13,233 prescriptions and 24,107 preparations, 577 events have been identified. 94% of the events were detected by the pharmacist. The most frequent errors concerned the prescription process and more particularly errors related to dosage (n = 167), treatment schema (n = 164) and patient parameters (n = 133).

Among the incidents reported, 21 had a repercussion on the patient or on the drug.

Conclusion: This study has enabled the pharmacy to identify the type of errors, their frequency and their severity. The 'cartography' obtained reveals an important proportion of prescription incidents and illustrates the central role of the pharmacist in their detection. The WHO-recommended taxonomy application offers the benefits of sharing the reports at a national level and dissemination of recommendation for improving medication patient safety.

Keywords: Chemotherapy, medication errors, monoclonal antibodies, patient safety

Introduction

Patient safety has become a priority for Belgian health authorities. A safety culture has been developed in which everyone has a permanent and active awareness of situations where errors are likely [1]. This creates an environment where it is accepted that institutions and healthcare providers may make mistakes, and processes and equipment may fail. The programme now promoted by Belgian health authorities encourages healthcare institutions to move from a culture of blaming individuals for errors to a non-punitive culture where errors are seen as opportunities to explore and learn from system failure [2].

Health care delivery is a complex process in which medication plays a key role. Failure may occur at any stage during the medication process; from the prescription of the drug, to its preparation, dispensing and administration.

The high toxicity of cancer drugs is well known and chemotherapy-related errors are still widely feared due to their potentially serious consequences. Problems with chemotherapy may arise from a lack of adherence to protocols, or may be associated with the chemotherapy itself or with inadequate concomitant care [3]. There are many reports in the literature of medication-related errors, highlighting the frequency and the severity of their consequences [4-6].

In recent years, the unique specificity of monoclonal antibodies has provided a novel approach to the treatment of malignancies, transplant rejection, autoimmune and infectious diseases. Numerous monoclonal antibodies are still under investigation and will emerge on the market. However, despite the quality of life improvement associated with monoclonal antibodies, immune reactions, skin toxicity, serum sickness and a range of adverse events have been observed [7-9]. Thus, the administration of this class of drug requires close surveillance and involves many healthcare professionals, including physicians, pharmacists and nurses. There is scarce data on the errors related to monoclonal antibodies in term of frequency, severity and cost.

In order to provide quality health care to their patients, physicians adapt their treatment strategies to suit new molecules appearing on the market. Traditional cytotoxic drugs used to treat cancer are often associated with efficacy and toxicity limitations. Monoclonal antibodies associated with chemotherapy are increasingly common and have improved treatment safety and outcome [10]. These factors make the medication process more complex and require up-to-date knowledge among healthcare professionals.

The use of oral chemotherapy is increasingly successful, although intravenous anticancer drugs remain first-line treatments. It is strongly recommended to prepare hazardous medications centrally in order to improve quality and minimize the

exposure of personnel to these drugs [11]. Some monoclonal antibodies are considered potentially harmful, and their handling and preparation is the responsibility of the pharmacist in charge of chemotherapy preparations.

Medication safety is integral to patient safety and, as experts in medication delivery, pharmacists play a central role in preventing and managing medication errors [12]. The objectives of this project were to identify targets for improving the administration of chemotherapy and monoclonal antibodies. A secondary objective was to assess the pharmacist's role in the development of a safety culture.

Methods

Study design and sample

The study was designed as a retrospective analysis of chemotherapy, monoclonal antibody and concomitant therapy-related incidents. The analysis was conducted in the Erasme Hospital, an 864-bed university hospital in Belgium. The institution has a centralized cytotoxic production unit in which treatments are prepared for medical oncology, haematology and rheumatology. The study focuses on day-care patients and hospitalized patients.

During the 24-month study period, more than 24,000 doses of chemotherapy and monoclonal antibodies were prepared. Handwritten prescriptions contained each patient's identification and location, treatment scheme, dose, date and conditions of administration. All prescriptions were completed by physicians, and patient parameters – weight, height, body surface area – were measured and calculated by nurses. The prescriptions were validated by the pharmacist using a database programme in which all prescriptions were registered, allowing the pharmacist to check patient data, previous treatment and adjustment or deviation from the therapeutic protocol.

Labels for perfusions were edited by the database programme and given with the prescription to pharmacy technicians for preparation. Prior to dispensing, all preparations were checked and validated by pharmacists.

Establishment of a medication errors reporting system

Further to a national safety programme, a safety campaign was organized by the safety team in the Erasme Hospital between 2008 and 2010 to alert healthcare professionals to patient safety. During this campaign, guidelines about which incident to report and how to do so were provided.

In collaboration with the patient safety team, a multidisciplinary group including the pharmacist in charge of cytotoxic production was created to establish a medication-error reporting system to report all incidents and near misses related to chemotherapy, monoclonal antibodies and concomitant treatments.

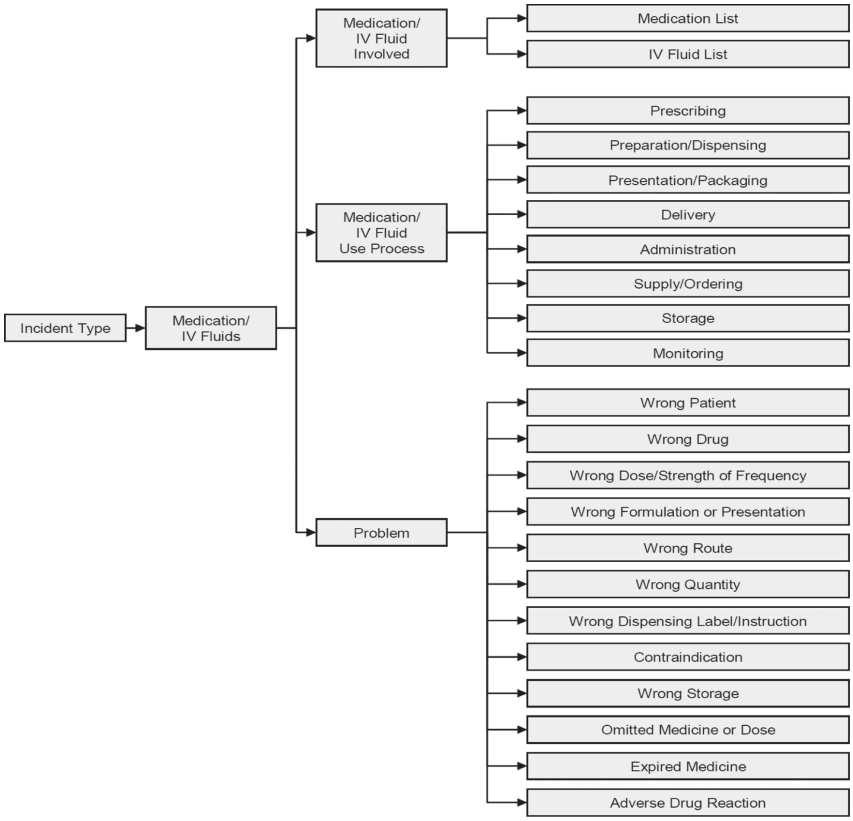
In order to identify steps prone to error, a detailed description of the entire chemotherapy ordering process was completed, from prescription to administration. To ensure the same language was used, some definitions were required. An incident is defined as any event or circumstance that could have resulted, or did result, in unnecessary harm to a patient. A 'near miss' is defined as a near incident, which did not reach the patient [13].

Medication incidents should not be confused with adverse drug reactions, which need to be reported within the pharmacovigilance system. According to the World Health Organization (WHO) taxonomy, patient safety is categorized into process and outcome. Those recommendations defined as 'process' and are the activities of providers for delivering care, while 'outcome' are the consequences of clinical activities by providers [14].

For each process identified, potential problems are described according to the WHO taxonomy, see Figure 1 [13].

Within the patient safety team, a database programme was created enabling users to collect, store and retrieve data in a reliable and organized way.

Figure 1: WHO medication/IV fluid problems [13]



Data reporting

All incidents and near misses reported by physicians, nurses and pharmacists were transmitted to the patient safety team and were treated and registered anonymously. To report an incident, the four following levels of information were required:

- Incident type (process/problems)
- Incident characteristic (origin, discovery, reporting)
- Patient outcomes
- Organizational outcomes

Other information could be provided but was optional.

In the study, overdosing and underdosing were defined as an extension of 5% from the recommended dose.

A patient outcome assessment was completed for each incident recorded. Patient outcome is defined as the impact upon a patient which is wholly or partially attributable to an incident. The degree of harm is described in Table 1 [15].

Organizational outcome is defined as the impact upon an organization that is wholly or partially attributable to an incident [15].

Data analysis

Among all incidents and near misses that occurred, chemotherapy, monoclonal antibodies and concomitant treatment-related events were analysed to identify process failure. The analysis focused on identifying conditions that led to the incident and on developing recommendations to decrease its occurrence.

Results

During the 24-month study period, 24,107 preparations were completed by the centralized cytotoxic production department: approximately 79% antineoplastic drugs and 21% monoclonal antibodies. In total, 80% of the prescriptions were for ambulatory patients, with 20% for hospitalized patients. Among the 13,233 prescriptions treated, 577 incidents and near misses were detected. An average of 24 errors per month was reported, see Figure 2.

Overall, 419 errors (73%) concerned antineoplastic agents, 140 errors (24%) concerned monoclonal antibodies and 18 (3%) were related to concomitant treatment, see Figure 3.

Among the 577 incidents reported, 540 (94%) errors were detected by the pharmacist, see Figure 4.

Using the WHO taxonomy, two topics were considered: medication liquid IV and documentation. For the intravenous therapy topic, three steps were identified. For both two topics, problems are described in Table 2.

The most frequent errors (n = 464) concerned the prescription process and more particularly errors related to dosage (n = 167), treatment schema (n = 164) and patient parameters (n = 133). Among the incidents reported, 21 had a repercussion on the patient. The degree of harm is described in Figure 5.

Among the 21 patient outcomes reported, 11 were due to documentation process failure.

Table 1: Patient degree of harm [13]

None	Patient outcome is not symptomatic or no symptoms detected and no treatment is required.
Mild	Patient outcome is symptomatic, symptoms are mild, loss of function or harm is minimal or intermediate but short term, and no or minimal intervention, e.g. extra observation, investigation, review or minor treatment, is required.
Moderate	Patient outcome is symptomatic, requiring intervention, e.g. additional operative procedure, additional therapeutic treatment, an increased length of stay, or permanent or long-term harm or loss of function.
Severe	Patient outcome is symptomatic, requiring life-saving intervention or major surgical/medical intervention, shortening life expectancy or causing major permanent or long-term harm or loss of function.
Death	On balance of probabilities, death was caused or brought forward in the short term by the incident.

Figure 2: Number of incidents reported per month

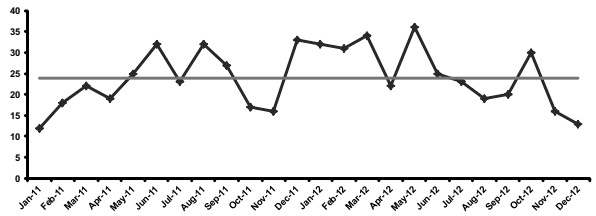


Figure 3: Number of prescriptions, preparations and incidents

Number of prescriptions	13233
Number of preparations	24107
Antineoplastic drug	19153
Monoclonal antibodies	4954
Number of incidents	577
Antineoplastic drug	419
Monoclonal antibodies	140
Concomitant treatment	18

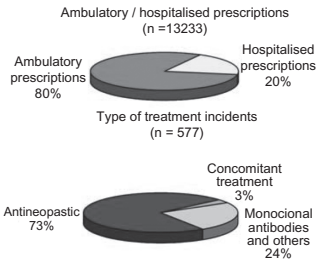


Figure 4: Percentage of notification made by pharmacists, nurses and physicians (n = 577)

Table 2: Problems recorded

Problems	Processes (%)			
	Prescribing	Preparation/ Dispensing	Administration	Documentation
Wrong dose/Stength of frequency (n = 464)	80.5	1.4	–	–
Patient parameters (n = 133)	23.1	–	–	–
Weight	6.4	–	–	–
Length	7.5	–	–	–
Weight and length	3.6	–	–	–
Body Area	5.4	–	–	–
AUC	0.2	–	–	–
Dose (n = 167)	29.0	–	–	–
Underdosing	16.3	–	–	–
Overdosing	12.7	–	–	–
Schema (n = 164)	28.4	–	–	–
Omitted medicine or dose	2.9	–	–	–
Day of treatment	7.5	–	–	–
Dose	16.3	–	–	–
Others	1.7	–	–	–
Wrong instruction	2.8	–	–	–
Wrong coding	–	0.7	–	–
Labelling	–	0.5	–	–
Wrong drug	2.3	0.7	0.3	–
Wrong patient	3.1	–	0.2	–
Wrong quantity	1.7	1.2	0.5	–
Wrong storage	–	0.3	–	–
Incompatibility	0.9	–	–	–
Wrong formulation or presentation	–	0.7	–	–
Wrong route	–	–	0.3	–
Forms/Certificates	–	–	–	1.9
Total	**91.3**	**5.5**	**1.3**	**1.9**

Discussion

This study has highlighted an error rate of 4.4%. However, most of the errors reported did not affect the patient. The percentage of intercepted and reported incidents by pharmacists demonstrates their role in patient safety improvement. Some of the incidents reported could have had fatal consequences for patients if they were not stopped.

Medication use process failure

Prescription errors were the most frequent errors and could be explained by the handwritten prescription process. During the study period, 17 antineoplastic drugs were prescribed with a dose double the recommended dose. Near incidents with doses 10 times higher were also observed.

The use of a computerized chemotherapy ordering system (CCOS) is well described in the literature to reduce medication errors [6, 16]. However, due to considerable variation among treatment schemes, complex CCOS implementation and incompatibility, or poorly available programmes, physicians still handwrite prescriptions [17].

Waiting for the computerization of prescription process, some corrective actions have been established. In collaboration with a haematologist and pharmacist, prescription order forms have been standardized for some haematological scheme treatments. This standardization should be extended to all prescriptions. Efforts should be made to ensure that correct patient parameters (weight, height, body surface) are indicated on the prescription. Weight tickets could be attached to prescriptions to ensure that a patient has been weighed on the treatment day.

Chemotherapy is commonly prescribed with concomitant care. Our pharmacy department prepares, for example, at least twelve different antiemetic drugs. In collaboration with pharmacists, a decisional drug algorithm should be written to standardize the concomitant treatment choice according to international guidelines.

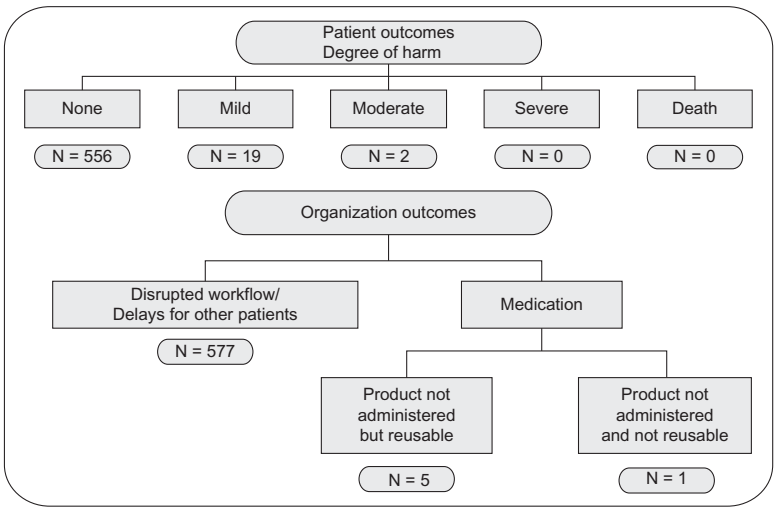
Within the preparation department, several actions were implemented to improve safety and quality. Those actions notably included centralization of chemotherapy and monoclonal antibodies, prescription validation by pharmacist, preparation protocol redaction, a double-check process and printed labels. Consequently, few incidents were observed within the preparation process. Some additional measures should be taken to further reduce preparation errors.

Concerning the administration process, nurses and physicians reported eight errors of administration. Bar code technology has been described as an important improvement of medication administration [18]. Its implementation should be approached by the multidisciplinary team.

Documentation process failure

Every year, numerous innovative drugs are reimbursed for cancer patients by the Belgian heath authorities. However, to

Figure 5: Patient and organization outcomes



obtain this reimbursement for their patients, physicians have to complete a certificate justifying the patient's need. Prior to dispensing those drugs, pharmacists are commonly in charge of verifying if reimbursement criteria are met.

For some drugs, the reimbursement request must be made to the relevant health insurance organization, which provides an authorization certificate prior to treatment. Consequently, this system generates an important documentation flow and can be a cause of errors. Our study has demonstrated that errors occurring through the documentation process could have consequences for patients. Eleven incidents were reported with a missing authorization of reimbursement for infliximab. Patients were consequently not treated and treatments were postponed for several weeks.

Monoclonal antibodies and new therapies

During the study, particular attention was assigned to monoclonal antibodies for which non negligible errors (n = 140) were also detected. Those emerging therapy errors require effective strategies to reduce their incidence. Continuing staff training and easy access to information are essential to integrate those drugs in daily routine.

Patient outcomes and establishment of a quality culture

Medical staff, pharmacy departments, wards and day-care units are involved in the use of chemotherapy and monoclonal antibodies. Depending on the degree of harm, a multidisciplinary approach could improve this process by the establishment of corrective actions.

Due to their involvement in the entire medication management system and their medication knowledge, including adverse effects, interactions, treatment schemes and reimbursement conditions, pharmacists occupy a strategic position to guide a multidisciplinary team. To do so, a committee was created including a pharmacist, an oncologist, a haematologist, a quality coordinator and a nurse. Elaborating therapeutic guidelines is one of the many objectives of the team to avoid patient harm. Chemotherapy training for healthcare providers needs special attention. The training programme should set out the content in modules [19]. A patient safety module should be created to educate employees to the safety culture and to alert them of unsafe processes.

The safety culture

Implementing a standardized medication errors reporting system allows the easier identification of errors and factors leading to their occurrence [1, 20].

The use of an international error-taxonomy offers the benefits of sharing the reports at a national level and dissemination of recommendations for improving medication patient safety. For example, following analysis of the literature describing errors related to the wrong route of administration for vincristine [17], we decided to abolish the syringe as a vehicle to administer vinca alkaloids.

The high number of incidents related to chemotherapy and monoclonal antibodies reported by the pharmacy has demonstrated that pharmacists were well aware of patient safety. The major limitation of this study is the low proportion of incidents and near misses reported by nurses and physicians. Further process failures could be identified by improving reporting levels among nurses and physicians. Results obtained should be used to alert even more nurses and physicians through the multidisciplinary team. A nationwide hospital survey on patient safety culture in Belgian hospitals has highlighted the need for a long-term national initiative implementation to improve patient safety [21].

Despite the corrective actions taken, a continual investment is required to improve patient safety.

Conclusion

Professional healthcare workers face an increasing number of cancer cases. With the increasing workload, they are confronted with the expanding variety of antineoplastic drugs and biological therapies, risks related to their handling and preparation, complexity of reimbursement conditions, high cost of cancer care, and risk due to serious consequences of medication errors.

This study illustrates the impact of a national safety programme and reveals that medication errors can occur at any stage of the chemotherapy process; allowing us to identify the type, frequency and severity of errors.

The findings reveal a significant proportion of prescription incidents, and demonstrate the central role of the pharmacist in their detection.

The implementation of a safety culture met with increasing interest and should be considered as an opportunity for pharmacists

to participate in quality improvement and medication safety initiatives. Ensuring safety in the health system is a multidisciplinary team effort in which the pharmacist's involvement is a key to guaranteeing the safe, effective and economic use of cancer drugs [12].

Medication errors should be considered as a quality indicator and should permit the adaptation of corrective measures. The implementation of a medication error system should be a priority for the oncology pharmacist.

Moreover, using the WHO recommended taxonomy offers the benefits of sharing the reports at an international level and disseminating recommendations for improving medication-related patient safety.

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Adherence to capecitabine chemotherapy

The development of new oral antineoplastic drugs has increased significantly in recent years, but patients on these drugs require as much advice as those on IV treatments. Monitoring adherence to capecitabine treatment may help prevent treatment failure and reduce adverse effects and costs.

Introduction

The burden of treatment administration is shifted to the patient when treated with oral antineoplastic therapy [1], a fact that comes with many challenges. The potential toxicity of anticancer agents, the recognition of adverse effects by the patient and their management, and the importance of patient's adherence for treatment success are important issues that have to be addressed [2].

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Capecitabine is an oral fluoropyrimidine that is usually given twice daily for two weeks followed by a one-week off medication. It is indicated for the treatment of breast, colorectal and gastric cancers [2].

Drug adherence (taking doses as prescribed) and persistence (no dose interruptions) with oral medications are critical to achieving the best clinical outcomes [3]. However, measuring patient adherence is a challenge, since there is no standardized methodology of measurement. The available strategies have some limitations, so two or more indirect techniques are frequently combined in the same study [4].

Adult patients with non-oncologic chronic diseases take only half of their prescribed medications on average [5]. However, cancer patients seem to be highly motivated due to the seriousness of their disease, and it is assumed that they have better adherence. Nevertheless, studies have shown that non-adherence to oral chemotherapy is still an issue [6]. According to published studies, adherence to oral chemotherapies is between about 16% and 100% [7].

Multidisciplinary patient care and patient education play a key role in successful oral anticancer treatment [2, 6]. Dispensing capecitabine in Hospital Pharmacy Departments is mandatory in Madrid, Spain, since February 2011 and represents 38% of dispensations of oral chemotherapeutics agents in our hospital. This fact represents a new challenge for hospital pharmacists who may play an active role in assessing, educating, and monitoring patients receiving oral antineoplastic therapy.

The aim of this study is to evaluate adherence in patients treated with capecitabine-based chemotherapy.

Method

A prospective cohort analysis was conducted between July and September 2011 in the Outpatient Unit of a Hospital Pharmacy Department.

Thirty patients treated with capecitabine, in monotherapy or in combination with other chemotherapeutic agents, were consecutively selected. Each patient was followed up for two to three months, through consecutive interviews carried out when patients came to the Pharmacy Department to collect their medication every 21 days. Data recorded were: personal details (age, gender, living situation, educational background and occupation); disease variables (tumour type, ECOG (Eastern Cooperative Oncology Group) performance status [8], disease onset and concomitant illness); treatment issues (type of treatment, line of chemotherapy, associated treatments, pill burden, duration of therapy and side effects); and drug adherence parameters.

A patient was considered to be adherent to treatment if an overall percentage of adherence ≥ 90% was achieved by three indirect methods – dispensing records, pill count and a validated questionnaire of adherence – Morisky-Green test [9], see Annex 1. Patients were asked for reasons for non-adherence in the interviews. Data collection sheets are shown as Annex 1.

Results

Thirty patients were included in this study. Fifty interviews were conducted (1.7 interviews/patient). Patient characteristics are listed in Table 1.

Twenty-seven patients (90%) were considered to be adherent. Three patients (10%) reported in one of their interviews some kind of compliance error. One of the patients was considered non adherent after checking drugs dispensing records and two did not answer the Morisky-Green test properly. Reasons for non-adherence were forgetting to take treatment and side effects like hand–foot erythrodysesthesia.

Discussion

Our results show that 90% of capecitabine-treated patients are considered adherent to therapy. These high rates of adherence with capecitabine are in accordance with other studies showing adherent patients rates between 70% and 91% [2, 3, 7, 10, 11].

We also found higher adherence rates relative to those with other chemotherapeutic agents such as tamoxifen [10]. This may be due to the relatively short treatment period of capecitabine, as adherence declines with time [12], and because of the more intensive multidisciplinary monitoring that is given to capecitabine-treated patients [10].

Table 1: Patient characteristics

	Number of patients	Percentage (%) of total patients
Personal Details		
Age (median ± SD, years)	66.2 ± 12.9	
Gender		
Male	22	73
Female	8	17
Living situation		
Familiar coexistence	27	90
Living alone	3	10
Educational background		
Higher education	11	37
Basic or no education	19	63
Occupation		
Healthcare related	0	0
Not healthcare related	30	100
Disease Variables		
Medical diagnosis		
Colon tumours	13	43
Rectum tumours	8	27
Breast cancer	5	17
Gastric cancer	2	7
Pancreas cancer	1	3
Unknown origin cancer	1	3
ECOG		
0	13	43
1	17	57
Disease onset [median, range (months)]	11 (3-216)	
Concomitant illness (median ± SD)	2.1 ± 1.95	
Treatment Issues		
Type of treatment		
Neoadjuvant	5	17
Adjuvant	10	33
Palliative therapy	15	50
Chemotherapy line of treatment		
First-line	18	60
Second-line	4	13
Third-line	4	13
Fourth-line	1	3
Fifth- Sixth-line	3	10
Associated treatments		
Monotherapy	19	63
Associated treatments (monoclonal antibodies, IV chemotherapy)	11	37
Pill burden (median ± SD, tablets/day)	11 ± 4	
Treatment time (median ± SD, months)	6.1 ± 2.9	
Side effects	20	67
Side effects (median ± SD, number)	1.4 ± 0.59	
Hand–foot erythrodysesthesia	10	33
Nausea	4	13
Diarrhea	3	10
Oral mucositis	3	10
Asthenia	2	7
Ocular dryness	2	7
Arterial hypertension	1	3
Dyspnea	1	3
Hyperbilirubinemia	1	3
Tachycardia	1	3

ECOG: Eastern Cooperative Oncology Group; SD: standard deviation.

Although adherence to oral anticancer therapy seems to be high, there are always a certain number of cancer patients who might need specific interventions to assure adherence [2]. For oral chemotherapy, pharmacy services are probably underused even in cancer centres [2]. Patient education by pharmacists can improve patient outcome and adherence to oral drugs as shown in a Cochrane review for diseases other than cancer [13]. In a recent study conducted by Simons et al. multidisciplinary pharmaceutical care intervention resulted in a significant improvement in patient adherence to capecitabine [2].

Adherence rates differ depending on the way they are measured, and results could be biased by altered behaviour when patients know they are being observed – the 'Hawthorne effect' [2].

There are different methods to measure adherence but each of them has considerable bias [5]. Self-reporting tends to overestimate adherence because patients are inclined to over-report their adherence to please their doctors. Counting pills gives no information about the timing of medication, and patients could be throwing away their pills. The analysis of prescription refills is not fully suitable for oral chemotherapy, which requires close monitoring of side effects and regular patient visits [3]. Therefore, we combined three methods of measuring therapeutic adherence in this study to minimize these biases as far as possible [4]. Furthermore, the adherence score applied in most studies (including ours) only takes into account the number of doses per day and not the interval between two doses and between meals [7].

The adherence limit of 90% that we established to define acceptable adherence is an arbitrary cut-off which is not based on any objective dose response data. We selected an adherence score of 90% instead of 80% due to the assumption that cancer patients should be more adherent than non-cancer patients because they are confronted with a serious life-threatening disease [3], but it would be desirable to define a universal 'adequate adherence' score as a result of dose-efficacy studies [2].

Annex 1: Adherence records – adherence questionnaire, pill count and dispensing records

Adherence questionnaire (Morisky-Green Test)
1. Do you ever forget to take drugs?
Yes No
2. Are you careless about the schedules?
Yes No
3. If you feel good, do you stop taking drugs?
Yes No
4. If you feel bad, do you stop taking drugs?
Yes No
To consider a good adherence, the answer to all questions must be appropriate (no, yes, no, no)

Pill count

Oral antineoplastic drug	Tablets consumed by the patient (CT) CT=DT-MT	Dispensed tablets (DT)	Missed tablets (MT) *Reason*	% ADH (CT/DT*100)
Total				

Dispensing records

Oral antineoplastic drug	Prescribed tablets/day	Days between dispensing	Total prescribed tablets (PT)	Dispensed tablets (DT)	% ADH (DT/PT*100)
Total					

The sample size of this study is not big enough to relate capecitabine non-adherence with factors influencing adherence. We are continuing to work with larger studies to determine the impact of factors that influence adherence.

In conclusion, our results show that most capecitabine-treated patients are highly adherent. However, there are specific patients with lower adherence rates that might benefit from pharmaceutical care.

Ethics approval: The project was approved by the Hospital Ramón y Cajal Ethics Committee.

Patient consent: All patients signed informed consent forms before entering the study.

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Analysis of environmental contamination in the central cytostatics department

Occupational exposure to antineoplastic drugs presents a serious threat in healthcare settings. We detected cytostatic environmental contamination in a hospital pharmacy using surface wipe testing, and demonstrated the efficacy of a 0.1 M NaOH decontamination solution.

Introduction

Special protective measures should be taken to avoid the potentially carcinogenic, teratogenic and mutagenic effects of cytostatic and cytotoxic drugs used in anticancer therapy. The installation of safety cabinets and appropriate ventilation systems, and the use of personal protective equipment and mixing devices can minimize the risk of exposure for healthcare workers who handle these drugs. Several studies [1-8] indicate that environmental contamination associated with handling cytostatics may still exist in the workplace despite compliance with these protective measures.

Zsuzsanna Órás, PharmD

To detect environmental contamination, a wipe sampling method was used. Wipe samples were collected from predefined sites and analysed with LC–MS for cytostatic drugs.

Monitoring cytostatic environmental contamination in the pharmacy at Bajcsy-Zsilinszky Hospital

Objective

The overall aim of this study was to evaluate cytostatic environmental contamination in the central cytostatic department of the hospital pharmacy using surface wipe – cytostatic wipe sample set by PharmaMonitor. Since there is no national data on cytostatic surface contamination in Hungary, we used the German reference value (0.1 ng/cm^2) as a reference. After the first analysis, a second test was performed to evaluate the efficacy of closed-system drug transfer devices and a new cleaning procedure, see Table 1.

Central cytostatics department

The pharmacy prepares 30–50 infusions per day for our two oncology departments (inpatient and outpatient). The oncology pharmacist checks and verifies individual therapies – selects, e.g. the right dose, medication, compatible infusion solution – and makes them ready to be transferred into the preparation area. In the preparation room, the background work is done by a pharmacy technician who makes the vials, bags and syringes ready, vents the infusion-sets and covers the bags if necessary with light protective foil.

Another pharmacy technician prepares the cytostatic infusions. The whole process is computer-aided by Cato software. After labelling the ready-to-administer infusions, they are delivered to the wards by transport personnel. At the end of the daily compounding session the laminar air flow (LAF) cabinet and the workbench have to be cleaned and disinfected by the technician while the rest of the surfaces, e.g. floor, door, furniture, are cleaned by the cleaning staff.

First sampling

The first samples were taken from five predefined areas in March 2011—LAF cabinet, workbench, floor in front of the LAF cabinet, transport box and the handle of the refrigerator located in the make-ready room. The samples were analysed for eight active ingredients – 5-fluorouracil (5FU), cyclophosphamide (CP), ifosfamide (IF), gemcitabine (Gem), etoposide (ETO),

Table 1: Comparison of test design, cleaning method and mixing devices

Difference in circumstances		1st Test (28/03/2011)	2nd Test (15/12/2011)
Method	Wipe test	✓	✓
Areas	LAF cabinet	✓	✓
	Workbench	✓	✓
	Floor	✓	✓
	Transport box	✓	✓
	Refrigerator handle (make-ready room)	✓	×
Cytostatic drugs	5-fluorouracil	✓	✓
	Cyclophosphamide	✓	✓
	Ifosfamide	✓	✓
	Gemcitabine	✓	✓
	Etoposide	✓	✓
	Methotrexate	✓	✓
	Paclitaxel	✓	✓
	Docetaxel	✓	✓
Decontamination solution	**0.1 M NaOH**	×	✓
Disinfection	70% IPA	✓	✓
Closed system	**PhaSeal**	×	✓*

*5-fluorouracil; methotrexate: PhaSeal was not used.

methotrexate (MTX), paclitaxel (Pac) and docetaxel (Doc) – with LC-MS/MS.

At the end of the work session the cabinet and workbench were wiped with 70% isopropyl alcohol (IPA), while the floor and the transport box were not cleaned before taking the samples.

Samples from the refrigerator handle were under the detection limit. The LAF cabinet was the most contaminated surface where the level of 5FU, Gem, MTX, CP were above the German reference value (0.1 ng/cm^2). Levels of IF and Doc contamination were similarly elevated, see Figure 1. Infusions containing IF were not prepared on the day of sampling and not even during the last six months. The levels of contamination on the other three surfaces are as follows: workbench > floor > transport box. 5FU, Gem and CP were detected at high levels on every surface except the refrigerator.

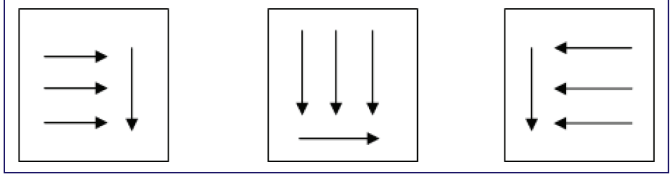
Improvements made in order to reduce contamination

The first sampling highlighted the weak points of the whole process. Improvements had to be considered: the most important was the implementation of PhaSeal closed system transfer device (CSTD). Many published studies [9-13] demonstrate the effectiveness of CSTDs in reducing cytostatic environmental contamination.

We did not use CSTDs during the preparation of MTX and 5FU infusions; the MTX vial is incompatible with the CSTD, and the extremely high number of 5FU vials used per month makes it impossible to finance the necessary number of CSTDs. Luer lock syringes are used for the preparation of these drugs.

The first results suggested that a simple disinfection method is not effective at removing contamination. A 0.1 M NaOH decontamination solution recommended by the analytical laboratory was implemented as a cleaning solution. The method of wiping is shown in Figure 2.

Figure 2: Method of wiping



Second sampling

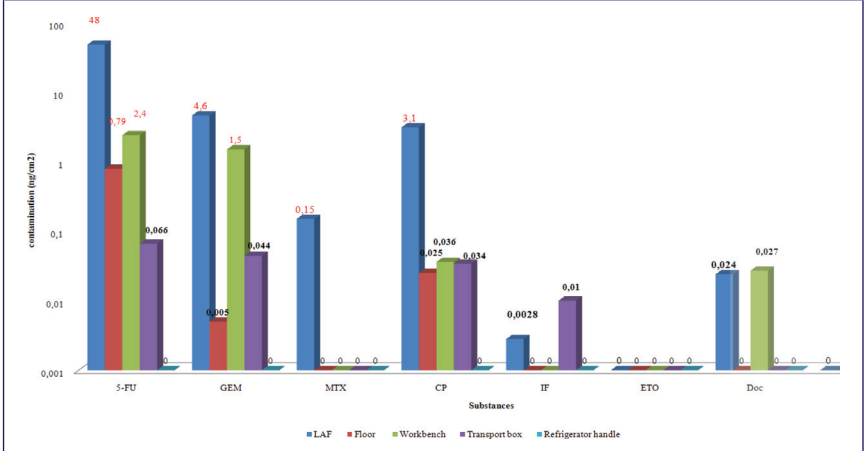
To check the efficacy of CSTDs, the new cleaning procedure and the usage of Luer lock syringes, we carried out a second wipe sampling after seven months using the same sampling method. The refrigerator was not analysed, but instead replaced by a new surface, the door handle of the preparation room.

The results from the four comparable surfaces—LAF cabinet, floor, workbench, transport box—are shown in Table 2.

After seven months a significant reduction was observed in the level of contamination on each surface, especially in the LAF cabinet, where four substances (MTX, CP, IF and Doc) were under the detection limit. This reduction underlines the efficacy of a 0.1 M NaOH decontamination solution. The previously very high level of 5FU was reduced by 80%, although it remained significant. The huge number of 5FU infusions prepared and the usage of Luer lock syringes and needles instead of CSTDs could explain this result.

The levels of 5FU and CP on the floor decreased, while the level of Gem increased. The cleaning of the floor performed by the cleaning personnel may not be sufficient to remove all of the contamination.

Figure 1: Levels of contamination during the first sampling, 28/03/2011*



*Values in red exceed those of the reference value (0.1 ng/cm^2). Values in black and bold represent the highest levels of contamination.
5FU: 5-fluorouracil; Gem: gemcitabine; MTX: methotrexate CP: cyclophosphamide; IF: ifosfamide; ETO: etoposide; Doc: docetaxel; Pac: paclitaxel.

The levels of Gem, CP and Doc detected on the workbench decreased, as well as the levels of Gem, CP and IF on the surface of the transport box.

Although CP could be detected in large quantities on every surface in March, it was under the detection limit in December.

There was an unexpected increase in the level of 5FU contamination on the workbench and transport box, and 5FU and Gem levels remained high on every surface. Inefficient cleaning procedure, contaminated gloves, and outside vial contaminations could be responsible for these results.

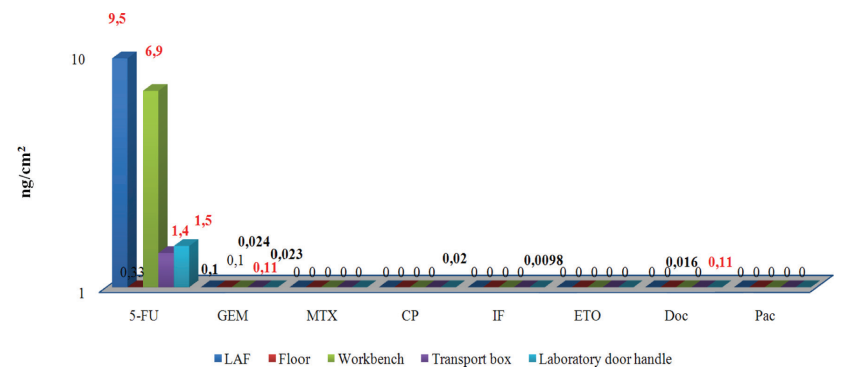
The levels of 5FU and Doc contamination on the door handle of the preparation room were above the reference value; Gem, CP and IF levels were also high, see Figure 3.

Table 2: Levels of contamination 28 March 2011 versus 15 December 2011

Substances	Contamination (ng/cm²)							
	LAF cabinet		Floor		Workbench		Transport box	
	28/03/2011	15/12/2011	28/03/2011	15/12/2011	28/03/2011	15/12/2011	28/03/2011	15/12/2011
5FU	**48**	**9.5**	**0.79**	**0.33**	**2.4**	**6.9**	**0,066**	**1.4**
Gem	**4.6**	**0.1**	**0.005**	**0.1**	**1.5**	**0.11**	**0,044**	**0.024**
MTX	**0.15**	**< 0.003**	< 0.004	< 0.003	< 0.004	< 0.004	< 0,004	< 0.005
CP	**3.1**	**< 0.003**	**0.025**	**< 0.003**	**0.036**	**< 0.004**	**0,034**	**< 0.005**
IF	**0.0028**	**< 0.003**	< 0.004	< 0.003	< 0.004	< 0.004	**0,01**	**< 0.005**
ETO	< 0.003	< 0.003	< 0.004	< 0.003	< 0.004	< 0.004	< 0.004	< 0.005
Doc	**0.024**	**< 0.007**	< 0.009	< 0.007	**0.027**	**0.016**	< 0.01	< 0.01
Pac	< 0.007	< 0.007	< 0.009	< 0.007	< 0.01	< 0.01	< 0.01	< 0.01

Green values: contamination decreased, red values: contamination increased, values in bold: high level of contamination.
5FU: 5-fluorouracil; Gem: gemcitabine; MTX: methotrexate CP: cyclophosphamide; IF: ifosfamide; ETO: etoposide; Doc: docetaxel; Pac: paclitaxel.

Figure 3: Levels of contamination during the second sampling, 15/12/2011[§]



[§]Values in red exceed those of the reference value (0.1 ng/cm²). Values in black and bold represent the highest levels of contamination.

Conclusion

Preventing occupational exposure to antineoplastic drugs is a priority in healthcare settings. Wipe sampling from the potentially contaminated environment can help us to evaluate preparation procedures and estimate the risk to healthcare workers.

The first sampling carried out in our hospital pharmacy proved the presence of certain cytostatic drugs in the preparation area.

The use of CSTDs can help prevent contamination during preparation; however it will not solve the problem of outside vial contamination.

A simple disinfection procedure is not effective at removing contamination from the surface; an appropriate decontamination solution has to be applied. The efficiency of a 0.1 M NaOH decontamination solution is remarkable, as demonstrated with drug preparations where we did not use closed-system devices.

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NEWS FLASH

Unplanned pregnancy during cancer treatment

A study from Amant's group shows the importance of thinking about contraception during cancer diagnosis and cancer treatment. Sarah van Peer and colleagues checked the database of the International Network for Cancer Infertility and Pregnancy (INCIP) for women who became pregnant during cancer diagnosis or during treatment.

The INCIP database currently includes 1,011 patients from 21 countries (at the time it included 897 patients).

Overall, 3.23% (29/897) of the patients in the database became pregnant after cancer diagnosis or during treatment. Of those 29 patients, three pregnancies were identified during diagnostic examinations for suspected malignancy but before definite diagnosis, 18 during treatment, and seven after cancer diagnosis but before treatment was started.

'The core message from our results is that it is vital for doctors and patients to discuss contraception during cancer diagnosis and cancer treatment. Although fertility issues are not the focus of attention at this time, it is necessary to provide advice about contraception. And although we know it's possible to treat patients with chemotherapy/radiotherapy during pregnancy when necessary, it's still better to avoid this situation, if possible."

Says Peccatori, 'Discussion about effective contraception remains a high priority for oncologists dealing with young patients with cancer. The incidence of unplanned pregnancy during cancer treatment probably remains a rare event. Nonetheless, the high emotional impact of an unplanned pregnancy and the possible maternal consequences in terms of treatment modification should prompt more effective interventions in this field.'

Source: ESMO 2014

Drug shortages hit US oncologists hard

References (please see article on pages 31–32)

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Studies on the stability and compatibility of cytotoxic drug infusions with the Tevadaptor device

Professor Graham Sewell, PhD; Milena Massimini

Abstract

Introduction: The role of closed-system drug transfer devices (CSDTD) in the preparation of cytotoxic infusions has attracted considerable interest in recent years. The use of such devices can subject drug infusions to contact with the materials used to construct the CSDTD, with potential implications for compatibility and stability of the drug. This study investigated the stability and compatibility of 11 frequently used cytotoxic drug infusions with the Tevadaptor device.

Methods: Test infusions of 11 cytotoxic drugs at clinically – relevant concentrations were prepared in either prefilled syringes (5) or infusion bags (6) and were stored under controlled conditions. The syringes and bags were divided into two groups; one group fitted with the Tevadaptor device (test), and a second group with no device fitted (controls). At predetermined times each infusion was sampled and subjected to testing for chemical and physical stability against defined acceptance criteria.

Results: In each case there was no difference between test and control groups in chemical or physical test data. The addition of the CSDTD did not influence the infusion stability.

Conclusion: The 11 cytotoxic drug infusions tested were compatible with the Tevadaptor device and infusion stability was not affected.

Keywords: Closed-system transfer device, compatibility, cytotoxic drugs, stability

Introduction

With continuing concerns about the risk of occupational staff exposure to cytotoxic drugs government agencies and special interest groups such as NIOSH (National Institute for Occupational Safety and Health) and ISOPP (International Society of Oncology Pharmacy Practitioners) have published guidelines [1, 2] on safe handling of these agents. The guidelines recommend use of containment devices such as biological safety cabinets or pharmaceutical isolators; and personal protective equipment such as nitrile gloves, chemo gowns and masks. In an attempt to provide further protection to the operator and the work environment, closed-system drug transfer devices (CSDTD) have been introduced to reduce the generation of aerosols during drug manipulations in hospital pharmacies. Several studies [3, 4] have been published showing the effectiveness of the CSDTDs in reducing work surface contamination with anticancer drugs and also in eliminating the risk of needle stick injuries to operators.

The use of a CSDTD places a new set of materials into contact with the cytotoxic drug infusion. This could influence the physical and chemical stability of the drug infusion and potentially leach compounds from the materials used in manufacture into the drug infusion. To ensure that safety and efficacy are maintained when using these devices it is essential that infusion stability and compatibility is established when a CSDTD is fitted.

The Tevadaptor is a CSDTD and comprises several components; a Vial Adaptor enables connection with drug vials. It contains the Toxi-Guard dual activated carbon and 0.2 micron membrane designed to allow sterile air to enter the vial and to trap drug vapours that may exit from it. The Syringe Adaptor fits standard Luer lock syringes and docks to the Vial Adaptor for syringe filling and to administration connecting sets for needle-free, closed-system administration to the patient. A Spike Port Adaptor connects to IV infusion bags and also docks to connecting sets for infusion administration. For pre-prepared infusions, the Syringe Adaptor (prefilled syringes) and the Spike Port Adaptor (infusion bags) could be in prolonged contact with cytotoxic infusions.

This study evaluated the compatibility of the Tevadaptor device with the following commonly used cytotoxic infusion:

- Carboplatin, cisplatin, etoposide, fludarabine, gemcitabine, irinotecan, and oxaliplatin; in infusion bags with Tevadaptor Spike Port Adaptor fitted.
- Doxorubicin, epirubicin, flourouracil and methotrexate; in prefilled syringes with Tevadaptor Syringe Adaptor fitted.

Test infusions with the CSDTD fitted, and Controls with no device fitted, were incubated under controlled conditions and sampled at various time intervals. The infusion concentrations were selected to be representative of typical clinical practice. Chemical testing included drug assay using stability-indicating HPLC assay and UV-visible spectroscopy to test for leaching of components into the infusion. Physical tests included sub-visual particulate testing, visual inspection, pH monitoring and gravimetric determination of moisture loss/gain. For each infusion the physical and chemical test data for the bags and syringes fitted with the CSDTD fitted (Test) were compared with data obtained for the Controls with no device fitted.

Methods and experimental design

Cytotoxic drugs were obtained as proprietary preparations from Teva UK, with the exceptions of epirubicin 2 mg/mL (Fresenius Kabi) and 5-fluorouracil 25 mg/mL (Hospira). All drugs were used within the manufacturers' expiry date. Luer lock polypropylene syringes (50 mL) were obtained from

Becton Dickinson and 250 mL infusions of 5% dextrose and 0.9% sodium chloride, in polyolefin bags, were obtained from Baxter Healthcare.

Test (+CSDTD) and Control (-CSDTD) infusions were prepared in duplicate for each drug included in the study. All test and control infusions were prepared by an experienced technician in a pharmaceutical isolator providing an EU Class A environment, and in accordance with the principles of good pharmaceutical manufacturing practice. Test syringes and infusion bags were fitted with the Tevadaptor Syringe Adaptor System or the Spike Port Adaptor, respectively. Control syringes were sealed with a conventional blind hub. Infusion concentrations, containers, diluents are shown in Table 1, together with storage conditions and sample times. Sampling times, and the duration of each stability/compatibility study was based on the authors' previous experience. Infusion samples were obtained from Control syringes and bags by removing the blind hub and dispensing or withdrawing infusion via the additive port with a syringe and needle, respectively. In the case of Test syringes a Luer lock adaptor was fitted to the Syringe Adaptor enabling the infusion to be dispensed from the syringe, and for infusions the samples were drawn from the Spike Port Adaptor after releasing the clamp. In each case this replicates the fluid-path experienced by infusions during clinical use.

At each sample time, the samples of both test and control infusions were subjected to the schedule of analysis described briefly below:

Drug assay by stability-indicating HPLC

The HPLC system consisted of a quaternary gradient pump (Jasco PU-2089 plus), an in-line degasser, autosampler (Jasco AS-2057 plus), and photodiode array detector (Jasco MD-2010 plus). Data were analysed with EZChrom Elite software (scientific software), version 3.1.7. Samples were injected in duplicate, bracketed with injections of the appropriate external standard. HPLC methods were fully validated (linearity of response, intra- and inter-day precision, stability-indicating ability using forced degradation studies where drugs were subjected to acid, base and oxidative stress at elevated temperature).

Acceptance criteria: Drug assay; assay value at each time point is within 95–105% of initial (t_0) value.

Specific details of each method and main validation data are outlined below:

Carboplatin, cisplatin and oxaliplatin: 250 × 4.6 mm Spherisorb CN 5 µm column, mobile phase of 0.005 M phosphate buffer pH 6.5 at 1 mL/min. Detection UV 205 nm.
Validation (carboplatin): Linear range 0.5–100 µg/mL, $R^2 = 0.999$. Intra-day and inter-day precision CV = 0.33% and 1.18%, respectively. Stability-indicating.
Validation (cisplatin): Linear range 0.5–100 µg/mL, $R^2 = 0.999$. Intra-day and inter-day precision CV = 1.3% and 1.7%, respectively. Stability-indicating.
Validation (oxaliplatin): Linear range 0.5–100 µg/mL, $R^2 = 0.999$. Intra-day and inter-day precision CV = 0.4% and 1.6%, respectively. Stability-indicating.

Doxorubicin, epirubicin: 250 × 4.6 mm Varian C18, 5 µm column, mobile phase of 0.005 M phosphate buffer pH 5:methanol:acetonitrile (40:30:30) with 0.6 g/L sodium dodecyl sulphate at 1 mL/min. Detection UV 232 nm.
Validation (doxorubicin): Linear range 0.01–10 µg/mL, R^2 = 0.999. Intra-day and inter-day precision CV = 1.1% and 1.3%, respectively. Stability-indicating.
Validation (epirubicin): Linear range 0.01–10 µg/mL, R^2 = 0.999. Intra-day and inter-day precision CV = 0.8% and 1.4%, respectively. Stability-indicating.

Etoposide: 250 × 4.6 mm Techsphere CN 5 µm column, mobile phase of water:acetonitrile (70:30) with 2.0 g/L sodium acetate at 1.5 mL/min. Detection UV at 285 nm.
Validation: Linear range 0.05–50 µg/mL, R^2 = 0.998. Intra-day and inter-day precision CV = 1.6% and 1.5%, respectively. Stability-indicating.

Table 1: Cytotoxic infusions included in study, container type, storage conditions and sampling schedule

Infusion and container	Storage conditions	Sampling times (days)
Carboplatin 2 mg/mL in 5% dextrose. 250 mL Polyolefin bag	2–8°C, protected from light	0, 7, 14, 28, 56, 84
Cisplatin 0.5 mg/mL in 0.9% NaCl. 250 mL Polyolefin bag	2–8°C, protected from light	0, 7, 14, 28
Doxorubicin 2 mg/mL undiluted. 50 mL Polypropylene syringe	2–8°C, protected from light	0, 7, 14, 28, 56, 84
Epirubicin 2 mg/mL undiluted. 50 mL Polypropylene syringe	2–8°C, protected from light	0, 7, 14, 28, 56, 84
Etoposide 0.25 mg/mL in 0.9% NaCl. 250 mL Polyolefin bag	20°C, protected from light	0, 2, 3, 5
Fludarabine 0.15 mg/mL in 0.9% NaCl. 250 mL Polyolefin bag	2–8°C, protected from light	0, 3, 7, 10, 14
5-Fluorouracil 25 mg/mL. Undiluted. 50 mL Polypropylene syringe	2–8°C, protected from light	0, 7, 14, 28, 56, 84
Gemcitabine 9 mg/mL in 0.9%NaCl. 250 mL Polyolefin bag	2–8°C, protected from light	0, 7, 14, 28, 56, 84
Irinotecan 1 mg/mL in 0.9%NaCl. 250 mL Polyolefin bag	2–8°C, protected from light	0, 7, 14, 28, 56, 84
Methotrexate 25 mg/mL. Undiluted. 50 mL Polypropylene syringe	2–8°C, protected from light	0, 7, 14, 28, 56, 84
Oxaliplatin 1.5 mg/mL in 5% dextrose. 250 mL Polyolefin bag	2–8°C, protected from light	0, 7, 14, 28, 56, 84

Fludarabine: 250 × 4.6 mm Techsphere ODS 5 µm column, mobile phase of 0.005 M phosphate buffer pH 6.5:methanol (85:15) at 1 mL/min. Detection UV 250 nm.
Validation: Linear range 0.1–50 µg/mL, R^2 = 0.999. Intra-day and inter-day precision CV = 0.3% and 1.1%, respectively. Stability-indicating.

5-Fluorouracil: 250 × 4.6 mm Luna C18 5 µm column, mobile phase of water:methanol (98:2) at 1 mL/min. Detection UV at 266 nm.
Validation: Linear range 1–100 µg/mL, R^2 = 0.999. Intra-day and inter-day precision CV = 1.7% and 2.0%, respectively. Stability-indicating.

Gemcitabine: 150 × 4.6 mm Gemini C18 5 µm column, mobile phase of water:methanol (95:5) with 4.1 g/L sodium acetate at 1 mL/min. Detection UV at 269 nm.
Validation: Linear range 0.1–100 µg/mL, R^2 = 0.999. Intra-day and inter-day precision CV = 0.8% and 1.7%, respectively. Stability-indicating.

Irinotecan: 250 × 4.6 mm Techsphere ODS 5 µm column, mobile phase of 0.01 M KH_2PO_4:methanol:acetonitrile:isopropanol (47:26:25:2) with 1.22 g/L sodium-1-decanesulfonate at 1.2 mL/min. Detection UV at 254 nm.
Validation: Linear range 1–100 µg/mL, R^2 = 0.998. Intra-day and inter-day precision CV = 0.9% and 1.9%, respectively. Stability-indicating.

Methotrexate: 250 × 4.6 mm Techsphere ODS 5 µm column, mobile phase of 0.005 M citrate-phosphate buffer, pH 6.0:acetonitrile:methanol (85:10:5) at 1 mL/min. Detection UV at 270 nm.
Validation: Linear range 1–100 µg/mL, R^2 = 0.999. Intra-day and inter-day precision CV = 1.4% and 1.5%, respectively. Stability-indicating.

pH measurement

A combination glass electrode and a GLP-compliant pH meter (Hanna pH 302 series) were first calibrated using standard reference solutions of pH 4.0, 7.0 and 10.0 before determination of infusion pH.

Acceptance criteria: any pH change is within ± 0.5 units of initial (t_0) value.

Weight change

Infusion bags and syringes were weighed before and after sampling on a calibrated analytical balance (KERN KB 10000-1) and the percentage weight increase/decrease on storage was calculated. Change in weight represents transfer of water vapour through the walls of the infusion container.

Acceptance criteria: Maximum weight change over a given storage interval is < 2%w/w. This test ensures that any water loss through the container walls does not mask drug loss due to degradation.

Sub-visual particulates

Sub-visual particle counts of infusions were conducted at predetermined time intervals in accordance with the Pharmacopoeial method using an LS-200/LiQuilaz AZ-E20 particle size analyser with APSS-view software, version 3.4 (Particle Measuring System Europe, UK). This was calibrated using certificated diameter latex spheres supplied by Particle Measurement Technique Ltd. The number of particles/mL at 10 and 25 µm were recorded for duplicate samples and the mean count of each was calculated. This analysis was used to detect particle growth in infusions, Pharmacopoeial standards were not applicable and, in view of the limited number of counts performed for each sample (n = 3), the counts obtained were considered to be semi-quantitatively only.

Acceptance criteria: < 5-fold increase in sub-visual particulate count/mL of both 10 and 25 µm diameter particles.

Visual inspection

Infusions were examined under ambient light against both white and black backgrounds for any change in colour, clarity or for the presence of particulate matter.

Acceptance criteria: no change in colour or clarity with respect to the initial (t_0) sample.

UV-visible scan

Infusions were diluted 1 to 10 with water and test infusions (+CSDTD) were scanned against a reference cell of the control infusion (-CSDTD) over the range 200–600 nm and any deviation from the baseline was recorded.

Acceptance criteria: deviation from baseline is < 0.05 au over entire scan.

Results

Chemical and physical data obtained for all infusions (Test and Control) were within the above acceptance criteria at all sample times in this study. The chemical and physical analysis data for the initial (t = 0) and final (t = x) sample time points for test and control infusions of each drug are summarized in Table 2. The small variations seen in pH and drug assay between initial and final sample – points was within normal experimental error and was not considered to be of pharmaceutical or clinical significance. Small increases in sub-visual particle counts were observed over time, but these occurred in both test and control infusions and, again, were within the predetermined acceptance criteria. Similarly, the visual appearance, UV-visible spectra and weight-change of infusions were all compliant with acceptance criteria at all sample points.

Discussion

As evidence on the effectiveness of CSDTD devices in reducing cytotoxic contamination continues to emerge [3, 4], the deployment of these devices is likely to increase, albeit at a slow rate because of financial issues. It is essential to demonstrate the containment effect of CSDTDs under actual practice conditions in pharmacy cytotoxic units and chemotherapy clinics. The

Table 2: Physical and chemical stability/compatibility data at initial (t = 0) and final sample points for 11 cytotoxic infusions in the presence (Test) and absence (Control) of the Tevadaptor device

Infusion	Test/Control sample time(d)	pH	Sub-visual particles/mL		Appearance/ Weight change/ UV-visual scan	Drug assay (% of initial value)
			10 µ	25 µ		
Carboplatin 2 mg/mL	Test 0	4.4	38	1.8	Complies	100 (1.9 mg/mL)
Infusion bag	Test 84	4.4	68	1.1	Complies	98.8
	Control 0	4.4	52	0.8	Complies	100 (1.9 mg/mL)
	Control 84	4.2	87	1.3	Complies	98.3
Cisplatin 0.5 mg/mL	Test 0	5.5	15	0.6	Complies	100 (0.48 mg/mL)
Infusion bag	Test 28	5.9	15	0.4	Complies	103.9
	Control 0	5.5	23	1.0	Complies	100 (0.50 mg/mL)
	Control 28	5.9	9	0.2	Complies	100.8
Doxorubicin 2 mg/mL	Test 0	2.7	27	1.1	Complies	100 (1.96 mg/mL)
Prefilled syringe	Test 84	2.6	36	0.9	Complies	97.3
	Control 0	2.7	35	0.8	Complies	100 (1.89 mg/mL)
	Control 84	2.6	41	1.2	Complies	98.9
Epirubicin 2 mg/mL	Test 0	3.9	39	0.7	Complies	100 (1.95 mg/mL)
Prefilled syringe	Test 84	4.1	62	1.2	Complies	100.8
	Control 0	3.9	26	0.2	Complies	100 (2.0 mg/mL)
	Control 84	4.2	52	0.9	Complies	98.8
Etoposide 0.25 mg/mL	Test 0	3.5	43	0.6	Complies	100 (0.25 mg/mL)
Infusion bag	Test 5	3.4	96	0.8	Complies	99.5
	Control 0	3.4	35	0.2	Complies	100 (0.24 mg/mL)
	Control 5	3.4	61	0.9	Complies	97.2
Fludarabine 0.15 mg/mL	Test 0	6.2	26	2.3	Complies	100 (0.15 mg/mL)
Infusion bag	Test 14	6.3	49	4.5	Complies	103.3
	Control 0	6.3	32	1.9	Complies	100 (0.15 mg/mL)
	Control 14	6.2	58	6.2	Complies	99.3
5-Fluorouracil 25 mg/mL	Test 0	8.9	57	1.0	Complies	100 (26.0 mg/mL)
Prefilled syringe	Test 84	8.9	37	0	Complies	97.6
	Control 0	8.9	32	0.4	Complies	100 (26.2 mg/mL)
	Control 84	8.9	28	0	Complies	96.4
Gemcitabine 9 mg/mL	Test 0	2.7	49	2.1	Complies	100 (8.95 mg/mL)
Infusion bag	Test 84	2.8	63	1.8	Complies	100.7
	Control 0	2.7	33	1.6	Complies	100 (8.81 mg/mL)
	Control 84	2.8	71	2.3	Complies	103.8
Irinotecan 1.0 mg/mL	Test 0	3.7	17	0.6	Complies	100 (0.99 mg/mL)
Infusion bag	Test 84	3.6	39	2.3	Complies	99.4
	Control 0	3.7	23	0.5	Complies	100 (1.01 mg/mL)
	Control 84	3.6	31	1.9	Complies	101.9
Methotrexate 25 mg/mL	Test 0	8.4	29	0	Complies	100 (25.1 mg/mL)

(*Continued*)

Table 2: Physical and chemical stability/compatibility data at initial (t = 0) and final sample points for 11 cytotoxic infusions in the presence (Test) and absence (Control) of the Tevadaptor device (*Continued*)

Infusion	Test/Control sample time(d)	pH	Sub-visual particles/mL		Appearance/ Weight change/ UV-visual scan	Drug assay (% of initial value)
			10 µ	25 µ		
Prefilled syringe	Test 84	8.6	53	1.0	Complies	101.5
	Control 0	8.4	30	0	Complies	100 (24.9 mg/mL)
	Control 84	8.7	51	0.7	Complies	101.6
Oxaliplatin 1.5 mg/mL	Test 0	7.1	39	0.2	Complies	100 (1.6 mg/mL)
Infusion bag	Test 84	7.0	38	2.1	Complies	97.4
	Control 0	7.1	28	1.5	Complies	100 (1.6 mg/mL)
	Control 84	7.1	21	1.9	Complies	98.1

Data shown are means of duplicate determinations. 'Complies' indicates compliance with stated acceptance criteria for weight change, visible appearance and UV-visible scans.

debate on whether a device is a 'fully closed-system' or not would seem of secondary importance to performance of the device in 'real-life'. However, before CSDTDs can be evaluated in the clinical setting, evidence is required to demonstrate that the device does not adversely affect the infusion or drug stability prior to administration to the patient. This study has evaluated the physical and chemical compatibility of the Tevadaptor device with 11 cytotoxic drug infusions with a view to facilitating evaluation of the device in pharmacy and clinical practice.

Tevadaptor Syringe and Spike Port Adaptors were challenged with a range of cytotoxic infusions, including those containing co-solvents to solubilize the drug (etoposide infusion) and infusions of low pH, e.g. gemcitabine and doxorubicin; and high pH, e.g. 5-fluorouracil and methotrexate. The schedule of testing was designed to identify any effect the CSDTD could have on drug stability, on damage to either the device or the container to which it was fitted resulting in the liberation of particulates or increased transfer of moisture (evidenced by weight change), change in pH, or the leaching of components such as pigments into the infusion that would absorb in the UV-visible region. The CSDTD and the containers used were not PVC-based so no specific tests were undertaken for plasticizers. In each case the CSDTD remained in contact with the infusion for the full, normally assigned shelf life under standard storage conditions. Overall, and to ensure rigour, the study design was compliant with the guidelines published in consensus report [5] of a European expert conference on cytotoxic stability.

For all of the infusions tested, and at all sample times, the infusions fitted with the appropriate Tevadaptor device, and the control infusions with no CSDTD fitted, were all within the stated acceptance criteria for each test. Furthermore, there were no significant differences observed between the test and control infusions in any of the physical and chemical tests deployed. This study has confirmed that under the normal storage conditions stated, the Tevadaptor Syringe Adaptor and Spike Port Adaptor were compatible with a range of commonly used cytotoxic infusions at typical drug concentrations. The fact that the long shelf lives assigned to these infusions were not compromised by the CSDTD suggests the device would be appropriate for use in centralized cytotoxic preparation units and for dose-banding schemes where extended stability is required [6]. We recommend that compatibility with drug infusions should be established for all CSDTD devices before they are introduced into clinical practice.

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Drug shortages hit US oncologists hard

Bea Perks, PhD

The number of drug shortages in the US has tripled between 2006 and 2012, with drug shortages now affecting most US oncologists and impacting on patient care. There is a need for new guidelines to control drug substitutions and to single out priority populations for relatively scarce drugs.

The very real threat of global drug shortages, particularly for cancer treatment [1, 2], shows little sign of abating. The impact of drug shortages on most oncologists in the US is affecting life-saving patient care, according to the findings of the largest study yet to quantify the impact of cancer drug shortages [3]. Of 250 board-certified US oncologists surveyed in late 2012 and early 2013, 83% reported facing a drug shortage in the past six months, and 92% of those said their patients' treatment had been affected.

'Our results indicate that the vast majority of oncologists in the country are facing wrenching decisions about how to allocate lifesaving drugs when there aren't enough to go around,' says the study's senior author, Dr Keerthi Gogineni [4]. 'The potential impact of these drug shortages is vast: they're putting patients at risk and driving up costs of cancer care,' adds Dr Gogineni, an instructor in the Division of Hematology-Oncology in the University of Pennsylvania's Abramson Cancer Center. The results of the study were presented at the American Society of Clinical Oncology (ASCO) Annual Meeting in June 2013 [3].

The shortages recorded in this study have had the greatest impact on drugs to treat paediatric, gastrointestinal and blood cancers, depriving physicians of standard chemotherapies to prescribe across a range of cancers. It is not clear exactly how these shortages will affect patient care, but the potential risks are clear. For example, if a drug has to be substituted while treatment is already underway, there might be no established dose equivalence or known safety profile when the substitute is combined with other therapies. There is also evidence of drug shortages holding back clinical trial progression.

Drug shortages are associated with increased costs; as the availability of a drug decreases, the price of that drug, and of its substitutes, increases. The availability of a drug can decrease for several reasons – as a result of manufacturing problems, or because the drug ceases to generate sufficient income for the manufacturer.

A critical production facility in the US was closed down in 2011 as a result of manufacturing and quality concerns [5]. The facility produced Johnson & Johnson's chemotherapy drug Doxil, which is used to treat ovarian cancer, multiple myeloma and AIDS-related Kaposi's sarcoma, and a generic injectable preservative-free methotrexate, which is used to treat children with leukaemia. The threat to patients was immense, causing the US Food and Drug Administration (FDA) to step in and approve the temporary importation of Sun Pharma Global's Lipodox (pegylated liposomal doxorubicin) from India as an alternative to Doxil, and to approve APP Pharmaceutical's generic injectable preservative-free methotrexate. To achieve this, FDA collaborated with industry, patients and their families, and other stakeholders.

Dr Gogineni and co-authors found that oncologists have had to substitute generics in short supply with more expensive branded drugs 60% of the time. In the case of shortages of generic 5-fluorouracil (5FU), 22% of physicians had to switch to the branded drug capecitabine, which costs about 140 times as much as 5FU for one round of colon cancer treatment.

The number of drug shortages in the US tripled between 2006 and 2012 [1]. New legislation that will require manufacturers to notify FDA six months in advance of any potential shortage is being drawn up in an effort to guard against future crises. However, the law does not impose penalties on companies that fail to warn FDA, prompting the chairman of ASCO's Government Relations Committee, Dr Richard L Schilsky, to question its value. 'If there's no teeth in that legislation some companies may decide not to report as required,' he warns.

Although drug shortages affect treatments for cancer the hardest, other diseases are also affected. Drugs for attention deficit hyperactivity disorder (ADHD), for example, faced severe shortages in the US in 2012 as a result of government regulations to prevent stockpiling [6]. ADHD drugs are addictive and are apparently popular with college students, who use them to get high or in order to get better exam results. Efforts by the US Drug Enforcement Administration to prevent this abuse have put children with ADHD at risk, according to patient groups and even FDA's own Drug Shortage Program.

Any system designed to warn regulators of impending shortages faces the hurdle of working against the interest of competing manufacturers. The Generic Pharmaceutical Association (GPhA), the US trade association for manufacturers and distributors of generic prescription drugs, recently developed an Accelerated Recovery Initiative (ARI), in response to the issue of drug shortages [7]. ARI supplies FDA with production planning and supply-chain information, but this could raise antitrust concerns if the information is shared between competing companies. For this reason, the information, services and technology company IMS Health is now an impartial third party to collect the data and provide FDA with a monthly report. The US Federal Trade Commission (FTC) approved ARI in August 2012, concluding that it would not be anticompetitive.

Following an executive order signed by President Obama in 2011 to address the problem of drug shortages [8], FDA reported that efforts to prevent shortages were beginning to take effect [9]. FDA Commissioner Ms Margaret Hamburg was quoted as being 'amazed and delighted' by the progress being made. According to FDA, it had prevented 128 drug shortages in the six months since the order was signed. Only 42 new drugs were reported to be in short supply in 2012, compared with 90 new shortages between January and April 2011.

Drug shortages are hampering patient care worldwide. In 2012, the results of a survey by the UK pharmacists' organization *Chemist+Druggist* revealed that the vast majority (95%) of pharmacists spend more than an hour a week trying to locate out-of-stock drugs [10]. In addition, most pharmacists (93%) regularly failed to receive drugs within 24 hours, which is the time stated in official guidance from the UK Department of Health.

The British Association of Pharmaceutical Wholesalers (BAPW), in line with the GPhA [7], has called on pharmacists and manufacturers to support objective monitoring and reporting of medicine supplies [11], although in this case the supply of brand-name drugs rather than generics. As with ARI and IMS, the need for an independent monitoring and survey service was highlighted. The BAPW noted 'inefficiencies' in the UK medicine supply chain, and has called for changes to, and enforcement of, regulation in this area.

In March 2013, Greece provided a stark reminder of the effect of national politics and financial stability on drug supplies [12]. Greece's drug regulator, the National Organization for Medicines, reported that foreign drugmakers had cut supplies to the country by 90%. The shortages are reported to affect treatments for arthritis, hepatitis C and hypertension, cholesterol-lowering agents, antipsychotics, antibiotics, anaesthetics and immunomodulators used to treat bowel disease. The severe drug shortages have been blamed on Greek debts and a fear of parallel trade (Greece's drug prices are at least 20% lower than the lowest prices in Europe, which is fuelling parallel trade).

Meanwhile, in Canada, the country's regulatory body Health Canada has blamed a growing drug shortages problem on bulk buying [13]. According to Health Canada, bulk-buying arrangements by the Canadian Government have caused companies to look beyond the relatively small Canadian market, sometimes leaving only one company supplying essential medicines. The danger of such an approach was brought home when the one company that supplied morphine, hydromorphone and fentanyl to the Canadian Government, Sandoz, stopped production following a fire at one of their plants. The country's research-based pharmaceutical companies (Rx&D) and the Canadian Generic Pharmaceutical Association (CGPA) have committed up to CA$100,000 each to address both immediate and long-term requirements to ensure that drug treatments are available when needed. The plan includes inventory tracking and the development of a system to report anticipated shortages.

While efforts to tackle drug shortages are clearly taking shape worldwide, there is considerable room for improvement. The authors of the University of Pennsylvania study revealing the harsh effects of drug shortages on US oncologists [3] highlight the pressing need for guidelines to control drug substitutions and to single out priority populations for scarce drugs.

'This is a dynamic problem, and when we learn about new shortages on the horizon, there is usually not a lot of time to plan for how to deal with them,' says Dr Gogineni. 'Guidelines must be rapidly updated and disseminated, both to large academic medical centers and smaller community hospitals and practices'.

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