RESEARCH ARTICLE

Cost Analysis of Using a Closed-System Transfer Device (CSTD) for Antineoplastic Drug preparation in a Malaysian Government-Funded Hospital

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Abstract

Background: Apart from reducing occupational exposure to cytotoxic hazards, the PhaSeal® closed-system transfer device (CSTD) can extend the beyond-use dates (BUDs) of unfinished vials of antineoplastic drugs for up to 168 hours (seven days). In this study, the total material cost incurred by its use in a Malaysian government-funded hospital was calculated. **Methods:** A list of vial stability following initial needle punctures of 29 commonly-used antineoplastic drugs was compiled. The amount of the materials used, including drugs, infusion bottles, the PhaSeal® CSTD and other consumables, was recorded on a daily basis for three months in 2015. The total cost was calculated based on the actual acquisition costs, and was compared with that of a hypothetical scenario, whereby conventional syringe-needle sets were used for the same amounts of preparations. **Results:** The use of the PhaSeal® CSTD incurred a cost of MYR 383,634.52 (USD 92,072.28) in three months, representing an average of MYR 170.5 (USD 40.92) per preparation or an estimated annual cost of MYR 1,534,538.08 (USD 368,289.14). Compared with conventional syringe-needle approach, it is estimated to lead to an additional spending of MYR 148,627.68 (USD 35,670.64) yearly. **Conclusion:** Although there was a reduction of drug wastage achieved by extending BUDs of unfinished vials using the PhaSeal® CSTD, cost saving was not observed, likely attributable to the wide use of lower-priced generic drugs in Malaysia. Future studies should further evaluate the possibility of cost saving, especially in health settings where branded and high-cost antineoplastic drugs are more commonly used.

Keywords: Antineoplastic agents- closed-system transfer device- cost savings - malaysia - occupational exposure.

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Introduction

The introduction of new medical technologies has constantly driven the growth in health expenditure, and is thus a concern for policymakers worldwide (Sorenson et al., 2013). Many health systems now require that ancillary benefits of a new technology justify its additional cost (Herndon et al., 2007). To date, Malaysia spends about 4% of its gross domestic product (GDP) equivalent of USD400 per capita on healthcare, with almost 98% of the total expenditure on public health services directly funded by the government (Hassali et al., 2013; Wong and Wickramasinghe, 2014). Therefore, in light of the increasing budgetary pressures, healthcare providers in Malaysia should extend their focus beyond the effectiveness of a new technology to consider the financial implications.

The presence of antineoplastic drugs in airborne and wipe samples from healthcare facilities has been well documented (Yoshida et al., 2011; Hedmer and Wohlfart, 2012). These hazardous drugs, which are primarily used for cancer treatment, are known for their carcinogenic and mutagenic properties (Ladeira et al., 2015). Additionally, immediate contact with antineoplastic drugs among women has been reported to increase the incidence of infertility, miscarriage, premature delivery and congenital malformation (Elshamy et al., 2010). The potential risk of long-term occupational exposure is also of concern, given that the antineoplastic drugs and their metabolites were consistently detected in the urine samples of healthcare workers (Yoshida et al., 2011; Yoshida et al., 2013). It is conceivable that direct handling of drugs is unavoidable during compounding and dispensing; therefore, pharmacy staffs are at high risk of exposure to the corresponding hazards (Hon et al., 2011).

To date, many measures have been taken to contain occupational exposure to cytotoxic hazards, some of which include the use of a Class II biological safety cabinet (BSC), an isolator and personnel protective equipment (PPE). Aside from that, closed-system transfer device (CSTD) is increasingly recognized as an engineering control to further limit the effects of occupational exposure (Connor and McDiarmid, 2006). CSTD is defined as a drug transfer device which can mechanically prevent the

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transfer of environmental contaminants into the system and the escape of vaporized drugs outside the system (Nygren et al., 2009). Currently, the use of CSTD in preparation of antineoplastic drugs is recommended by the National Institute for Occupational Safety and Health (NIOSH) (2004), the American Society of Health-System Pharmacists (ASHP) (2006), and the International Society of Oncology Pharmacy Practitioners (ISOPP) (2007).

In particular, the utilization of the PhaSeal® CSTD (BD Medical) has been shown to effectively reduce environmental contamination during antineoplastic drug preparation (Harrison et al., 2006; Nishigaki et al., 2010; Sessink et al., 2011; Favier et al., 2012; Sessink et al., 2013). Moreover, it has advantages over other CSTDs due to its ability to reduce microbial contamination of vials following multiple entries (De Prijck et al., 2008). The United States Pharmacopeia (USP) (2008) mandates that a single-use vial should be used within six hours following the initial needle puncture if maintained in an ISO 5 environment; nevertheless, evidence has indicated that the PhaSeal® CSTD is able to preserve sterility of a vial to which it is attached for up to 168 hours (seven days) under the similar conditions (Carey et al., 2011; Forrey et al., 2011). Two previous studies also demonstrated that cost saving, in the range of USD 600,000 and USD 800,000, could be achieved by using the PhaSeal® CSTD to extend the beyond-use dates (BUDs) of opened vials (Rowe et al., 2012; Edwards et al., 2013).

The PhaSeal® CSTD has been routinely used among a number of public health facilities in Malaysia in order to minimize the risk of occupational exposure, even though such a safety measure is not mandatory (Keat et al., 2013). Nevertheless, there is very limited information regarding its impact on the healthcare system, particularly from the economic perspective. Equally of concern is the continually rising healthcare cost which is mainly borne by the Malaysian government, leading to the need for economic analysis of high-cost devices (Yu et al., 2008). This aim of this study was to determine the total material cost incurred by antineoplastic drug preparation in a government-funded hospital, with the BUDs of unfinished vials extended up to seven days by using the PhaSeal® CSTD.

Materials and Methods

Ethics Approval

The study protocol was registered with the National Medical Research Register, Malaysia (ID: NMRR-15-1509-27629), and approved by the Medical Research Ethics Committee, Malaysia.

Setting

This study was undertaken in the Sultanah Bahiyah Hospital, Alor Setar, which was an 856-bed, tertiary medical center under the Ministry of Health, Malaysia. The Oncology Pharmacy Unit of the hospital was staffed by two pharmacists and one pharmacy technician specifically trained in antineoplastic drug preparation. This unit supported both inpatient and outpatient oncology services provided by various departments, ranging from Hematology, Obstetrics and Gynecology, Surgery, Respiratory Medicine to Pediatrics. It is operated two sessions (morning and afternoon) per day, including the weekends and public holidays. Approximately 10 prescriptions were received and 25 parenteral doses were dispensed daily in 2015.

Compiling the List of Commonly-used Drugs

Prior to data collection, a total of 29 antineoplastic drugs packaged in vials and commonly used in the Sultanah Bahiyah Hospital, Alor Setar, were identified (Table 1). The vial stability following initial needle punctures was compiled based on the existing literature (Gahart and Nazareno, 2008; the United States Pharmacopeial Convention, 2008; Carey et al., 2011; Forrey et al., 2011; Edwards et al., 2013; the BC Cancer Agency, 2016a; the BC Cancer Agency, 2016b). Generally, the vial stability with and without the use of the PhaSeal® CSTD was determined as seven days and six hours, respectively, except for those with a shorter stability period following reconstitution (the United States Pharmacopeial Convention, 2008; Carey et al., 2011; Forrey et al., 2011).

The Use of the PhaSeal® CSTD in Antineoplastic Drug Preparation

All injectable antineoplastic drugs were compounded in a Class II BSC by using aseptic techniques, with a Grade B cleanroom on a par with the requirement of the ISOPP (2007) as the background environment. Instead of using conventional syringe-needle sets, several components of the PhaSeal® CSTD have been utilized for drug preparation since the cleanroom started to operate in 2011. During each drug preparation session, PhaSeal® protectors (P50, P21 or P14) were attached to all vials which were ready to be used, and dates and times of opening were immediately recorded at each vial. PhaSeal® injectors (N35) containing 18-gauge needles were connected to luer-lock syringes, which were then used to transfer the vial content into infusion bottles via the built-in chambers of PhaSeal® adaptors (C100). Additionally, PhaSeal® injectors (N35) were used to create a leakproof seal for preparations in syringes, which were to be administered as subcutaneous, intramuscular, intravesical or intravenous bolus injections. During the study period, the unused portions of vials were kept in the cleanroom for a certain allowable duration as listed in Table 1; these partially-filled vials were kept in the cleanroom and, where possible, used for subsequent doses before opening a new vial.

Data Collection

Data were collected over a three-month period from 1st of October to 31st of December 2015. A standard data collection form was constructed to gather the following information on a daily basis: (i) the medications used; (ii) the number of preparations compounded; (iii) the number of vials opened; (iv) the total amount (mg) of medications used; (v) the number of infusion bottles used; and (vi) the number of each consumable item including the PhaSeal® CSTD used. All recordings were performed by the same investigator (Lim YM) at the beginning of each drug preparation session.

Cost Analysis

Data were tabulated and analyzed by using the Microsoft Excel 2010 (Microsoft, Washington). The scope of the material costs incorporated into the calculation included medications, infusion bottles and consumables (e.g. the PhaSeal® CSTD, syringes) used during the study period. The calculation was based on the actual acquisition costs, and the results were presented in Malaysian Ringgit (MYR), whereby MYR 1 was equal to USD 0.24 at the time of data analysis (February 2016). The total material cost incurred by the use of the PhaSeal® CSTD to prepare antineoplastic drugs was then compared with that of a hypothetical scenario, in which assumptions were made that: (i) conventional syringe-needle sets were used to compound the same amount of preparations; (ii) unused portions of vials were kept for only up to six hours following initial needle punctures (Table 1); (iii) Mini-Spike® dispensing pins (B. Braun Medical) were used to assist in withdrawing medications from vials; and (iv) Combi-Stopper closing cones (B. Braun Medical) were used to provide sterile closing for preparations in syringes.

Results

Total Cost of Drug Preparation

The costs of all materials used for drug preparation are shown in Tables 2 and 3. Overall, 900 prescriptions were received and 2250 preparations were compounded over the three-month study period (Table 2). The most frequently prescribed antineoplastic drug was fluorouracil (34%), followed by cyclophosphamide (8.7%) and cytarabine (7.4%). The total material cost of drug preparation using the PhaSeal® CSTD was MYR 383,634.5 (USD 92,072.3), which was 10.7% (MYR 37,156.9/ USD 8917.66) higher than that of the hypothetical scenario (MYR 346,477.6/ USD 83,154.6). The cost also represents an average of MYR 170.5 (USD 40.92) per preparation, and an estimated annual cost of MYR 1,534,538.08 (USD 368,289.14). Compared with the conventional needle-syringe approach, using the PhaSeal® CSTD to prepare antineoplastic drugs

Table 1. The List of Commonly-Used Antineoplastic Drugs and Their Vial Stability after Initial Needle Punctures, with and without the PhaSeal® CSTD

Drugs	Brands	Content per vial (mg/ units)	Vial Stability	
			With CSTD	Without CSTD
Bendamustine	Generic	100.0	30 minutes	30 minutes
Bleomycin	Generic	15.0	7 days	6 hours
Bortezomib	Velcade®	3.5	7 days	6 hours
Carboplatin	Generic	450.0	8 hours	6 hours
Cisplatin	Generic	50.0	2 days	6 hours
Cyclophosphamide	Generic	1,000.0	6 days	6 hours
Cytarabine	Generic	1,000.0	7 days	6 hours
Dacarbazine	Generic	200.0	4 days	6 hours
Daunorubicin	Generic	20.0	7 days	6 hours
Docetaxel	Generic	80.0	7 days	6 hours
Doxorubicin	Generic	50.0	7 days	6 hours
Epirubicin	Generic	500	7 days	6 hours
Etoposide	Generic	100.0	7 days	6 hours
Fluorouracil	Generic	1,000.0	7 days	6 hours
Gemcitabine	Generic	1,000.0	7 days	6 hours
Idarubicin	Generic	10.0	7 days	6 hours
Ifosfamide	Generic	1,000.0	7 days	6 hours
Irinotecan	Generic	100.0	7 days	6 hours
L-asparaginase	Generic	10,000.0	8 hours	6 hours
Liposomal doxorubicin	Caelyx®	20.0	7 days	6 hours
Mitomycin-C	Generic	10.0	7 days	6 hours
Mitoxantrone	Generic	20.0	7 days	6 hours
Methotrexate	Generic	500.0	7 days	6 hours
Oxaliplatin	Generic	50.0	7 days	6 hours
Paclitaxel	Generic	300.0	2 days	6 hours
Pemetrexed	Alimta®	500.0	7 days	6 hours
Vinblastine	Generic	10.0	7 days	6 hours
Vincristine	Generic	1.0	7 days	6 hours
Vinorelbine	Generic	50.0	3 days	6 hours

CSTD, closed-system transfer device

Table 2. Cost Comparison for Non-Medication Materials: Using the PhaSeal® CSTD Versus Conventional Needle-Syringe Methods (Hypothetical Scenario).

Drugs	Number of preparations	Costs (MYR)		Cost differences (MYR)[c]	Cost differences (%)[c]
		With CSTD[a]	Without CSTD[b]		
Bendamustine	1	68.5	22.0	46.5	211.5
Bleomycin	24	1,153.3	373.5	779.8	208.8
Bortezomib	36	1,104.8	120.6	984.2	816.1
Carboplatin	85	4,119.3	783.5	3,335.8	425.8
Cisplatin	113	6,069.0	1974	4,095.0	207.4
Cyclophosphamide	196	7,594.6	2,334	5,260.6	225.4
Cytarabine	166	7,566.0	2,516.6	5,049.4	200.6
Dacarbazine	17	1,742.0	315.0	1,427.0	453.0
Daunorubicin	6	608.3	230.5	377.8	163.9
Docetaxel	36	1,963.5	667.6	1,295.9	194.1
Doxorubicin	95	2,826.5	1,269.5	1,557.0	122.6
Epirubicin	82	4,887.6	1,703.5	3,184.1	186.9
Etoposide	83	3,394.4	1,087.5	2,306.9	212.1
Fluorouracil	765	24,523.8	6,819.0	17,704.8	259.6
Gemcitabine	92	5012.6	1,764.0	3,248.6	184.2
Idarubicin	5	222.4	114.5	107.9	94.3
Ifosfamide	6	493.3	172.5	320.8	186.0
Irinotecan	29	2413.5	882.5	1531.0	173.5
L-asparaginase	10	464.7	58.7	406.0	691.6
Liposomal doxorubicin	4	404.3	144.0	260.3	180.8
Mitomycin-C	5	325.5	126.7	198.7	156.8
Mitoxantrone	14	680.9	205.0	476.0	232.2
Methotrexate	37	3,105.1	1,177.0	1,928.1	163.8
Oxaliplatin	61	4,786.1	1,779.0	3,007.1	169.0
Paclitaxel	132	5,272.8	1,561.0	3,711.8	237.8
Pemetrexed	8	509.5	164.5	345.0	209.7
Vinblastine	26	789.8	274.1	515.7	1,88.1
Vincristine	91	3,079.5	175.8	2,903.6	1,651.2
Vinorelbine	25	1,091.7	301.0	790.7	262.7
Total	2,250	96,273.6	29,117.2	67,156.4	230.6

CSTD, closed-system transfer device; MYR, Malaysian Ringgit; [a]Consisting of costs for infusion bottles; luer-lock syringes and the PhaSeal® CSTD; [b]Hypothetical scenario; consisting of costs for infusion bottles;, luer-lock syringes; needles, Mini-Spike® dispensing pins; and Combi-Stopper closing cones; [C]Representing additional costs (MYR and %) incurred by the use of the PhaSeal® CSTD.

in a Malaysian government-funded hospital is estimated to incur an additional cost of MYR 148,627.7 (USD 35,670.6) every year.

Specific Medication and Non-medication Costs

Approximately 75% of the total expenditure on the materials was contributed by medications (MYR 287,360.9/ USD 68,966.62), but only 25 % was contributed by infusion bottles and consumable items including the PhaSeal® CSTD (MYR 96,273.62/ USD 23,105.67). Fluorouracil accounted for 25.5% of the expenditure on non-medication materials (MYR 24,523.78/ USD 5885.71), while bortezomib, pemetrexed and liposomal doxorubicin contributed to 54.9% of the total medication cost (MYR 157,623.35/ USD 37,829.6). Three-month use of the PhaSeal® CSTD resulted in a total medication cost of MYR 287,360.9 (USD 68,966.62), representing a 10.5% cost saved from potential drug wastage caused by the use of conventional syringe-needle sets. Nevertheless, it was found that using the PhaSeal® CSTD led to a 230.6% higher spending on non-medication materials compared with the conventional syringe-needle methods (MYR 96,273.62/ USD 23,105.67 versus MYR 29,117.2/ USD 6988.13).

Discussion

To the investigators' knowledge, this is the first study in Malaysia to provide a cost analysis for the utilization of the PhaSeal® CSTD, a high-cost device which has been claimed to be cost saving due to its ability to preserve the vial stability of antineoplastic drugs for up to seven days, besides limiting the occupational exposure to cytotoxic hazards (Harrison et al., 2006; Nishigaki et al., 2010; Carey et al., 2011; Forrey et al., 2011; Sessink et al., 2011; Favier et al., 2012; Sessink et al., 2013). The findings

Table 3. Cost Comparison for Medications: Using the PhaSeal® CSTD Versus Conventional Needle-Syringe Methods (Hypothetical Scenario).

Drugs	Total dosage (mg/ units)	Number of vials opened		Costs (MYR)		Cost differences (MYR)[b]	Cost differences (%)[b]
		With CSTD	Without CSTD	With CSTD	Without CSTD[a]		
Bendamustine	150	2	2	1,164.0	1,164.0	0.0	0.0
Bleomycin	444	33	35	5219.6	5,535.9	316.2	6.1
Bortezomib	75	27	32	77,139.0	91,424.0	14,285.0	18.5
Carboplatin	34,625	95	95	7,118.3	7,118.3	0.0	0.0
Cisplatin	7,608	164	179	2,481.3	2,708.3	226.9	9.1
Cyclophosphamide	157,850	158	184	4,594.6	5,350.7	756.1	16.5
Cytarabine	217,075	219	245	4,903.4	5,485.5	582.1	11.9
Dacarbazine	9,770	52	56	3,049.8	3,284.4	234.6	7.7
Daunorubicin	447	23	25	1,228.9	1,335.7	106.86	8.7
Docetaxel	4,040	53	61	7,739.1	8,907.2	1,168.16	15.1
Doxorubicin	3,743	75	96	2,010.0	2,572.8	562.8	28.0
Epirubicin	7,705	155	171	14,098.8	15,554.2	1,455.4	10.3
Etoposide	7,710	79	89	1,577.63	1,777.3	199.7	12.7
Fluorouracil	452,575	458	485	10,607.7	11,232.6	624.9	5.9
Gemcitabine	142,320	144	168	11,904.5	13,888.6	1,984.1	16.7
Idarubicin	97	12	12	8,994.8	8,994.8	0.0	0.0
Ifosfamide	14,650	15	17	701.5	795.1	93.5	13.3
Irinotecan	8,410	86	93	4,931.24	5,332.6	401.4	8.1
L-asparaginase	76,100	10	10	3,990.4	3,990.4	0.0	0.0
Liposomal doxorubicin	290	16	16	29,242.4	29,242.4	0.0	0.0
Mitomycin-C	140	14	14	3,482.5	3,482.5	0.0	0.0
Mitoxantrone	265	16	18	10,156.3	11,425.9	1,269.5	12.5
Methotrexate	49,925	104	121	2,895.4	3,368.6	473.3	16.3
Oxaliplatin	8,440	169	184	5,577.0	6,072.0	495.0	8.9
Paclitaxel	26,341	98	114	4,990.0	5,700.0	710.0	14.2
Pemetrexed	5,940	15	16	51,241.9	54,658.1	3,416.1	6.7
Vinblastine	230	25	26	2,191.2	2,278.9	87.6	4.0
Vincristine	119	120	130	2,201.1	2,488.2	287.1	13.0
Vinorelbine	897	22	25	1,928.3	2,191.2	262.9	13.6
Total	-	2,459	2,719	287,360.9	317,360.4	29,999.6	10.4

CSTD, closed-system transfer device; MYR, Malaysian Ringgit; a Hypothetical scenario; b Representing medication costs (MYR and %) saved by using the PhaSeal® CSTD.

could be useful to develop an economic framework to forecast costs incurred by its use in oncology practice.

Unlike two previous studies, this study demonstrated that cost saving was not realized by using the PhaSeal® CSTD to extend BUDs of vials (Rowe et al., 2012; Edwards et al., 2013). This may be attributed mainly to the lower prices of generic cancer drugs, which are widely used across health settings in Malaysia. Of 29 commonly-used drugs included in this study, 26 (89.7%) were purchased from generic manufacturers. It is also noteworthy that the remaining three branded drugs, bortezomib (Velcade®), pemetrexed (Alimta®) and liposomal doxorubicin (Caelyx®), contributed to more than half of the total drug expenditure. Therefore, the possibility of cost saving by using the PhaSeal® should be further investigated, especially in hospitals where branded drugs are more frequently used, or where more unfinished vials of high-cost items are conserved and used for subsequent preparations.

Besides, in this study, cost comparison was made between the use of the PhaSeal® CSTD and a hypothetical scenario, in which conventional drug compounding methods were applied. Previous studies focused merely on the costs saved from extending BUDs of vials, which are potentially sufficient to offset the cost of purchasing the PhaSeal® CSTD; nonetheless, the use of materials other than medications and CSTD, such as syringes, needles, infusion bottles and dispensing pins, was not considered in the cost analysis of those studies (Rowe et al., 2012; Edwards et al., 2013). Therefore, the current study provides a new perspective on calculating the material costs of conventional syringe-needle methods, which tend to be undervalued.

Nevertheless, it is noteworthy that the cost estimate

of this study could be conservative, as a number of opened, partially-filled vials were still unexpired at the end of the study period. As a result, the potential savings accomplished by reusing these vials during the subsequent drug preparation sessions was not reflected in the final calculated costs. Furthermore, the drug wastage resulting from extending BUDs of vials might be overestimated, as only large-volume vials, especially of medications with high unit costs (e.g. pemetrexed 500mg per vial), were used during the study period. Such wastage could be further reduced if vials of multiple sizes were used, thus leaving the smallest amount of unfinished vials remaining at the end of each drug preparation session.

This study did not include monoclonal antibodies, such as rituximab and bevacizumab, which are also extensively used in Malaysia. These drugs hold great promises for the treatment of a variety of malignant diseases, but have been imposing a substantial financial burden on the health system due to the high manufacturing costs (Samaranayake et al., 2009). Although most of these drugs are not cytotoxic and hazardous in nature, the use of the PhaSeal® CSTD to extend their BUDs in a 335-bed teaching medical center has been estimated to lead to a potential annual saving of nearly USD 500,000 (Edwards et al., 2013). Hence, further studies on the usefulness of CSTD in compounding monoclonal antibody preparations are needed, especially those addressing its impact on the healthcare expenditure in Malaysia.

In conclusion, although there was a noticeable reduction of drug wastage achieved by extending the BUDs of vials, the utilization of the PhaSeal® CSTD in a Malaysian government-funded hospital did not lead to cost saving, likely due to the high usage of lower-priced generic drugs. Future studies should further investigate the potential of cost saving in health facilities where branded and high-cost drugs are more commonly used.

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