Availability of WHO Essential Medicines for Cancer Treatment in Botswana

abstract

Purpose Stock outs of cancer drugs are potentially fatal but have not been systematically studied in low- and middle-income countries. The aim of this study was to determine the availability and alignment of the Botswana National Essential Medicines List (NEML) for cancer drugs with the WHO's Essential Medicines List (EML).

Methods The availability and cost of cancer drugs were analyzed using data from a weekly stock catalog sent by Botswana's Central Medical Store to all pharmacy departments in government hospitals. Comparative data were extracted from the WHO EML and the "International Drug Price Indicator Guide-2014" from the Management Sciences for Health. Interviews with key informants were used to collect data on the Botswana NEML and the drug supply chain in the public sector.

Results The 2015 Botswana NEML for cancer had 80.5% alignment with the WHO EML. At least 40% of essential drugs were out of stock for a median duration of 30 days in 2015. Stock outs affected chemotherapy drugs included in first-line regimens for treating potentially curable diseases such as cervical, breast, and colorectal cancer and were not associated with buyer price of therapy. Analyses showed that the median price ratio for procured drugs was greater than 1 for 61% of the NEML drugs, which suggests inefficiency in procurement in the public sector.

Conclusions Botswana has one of the highest alignments of NEML to the WHO EML in the sub-Saharan African region, which is consistent with investment in the health care system evident in other clinical spheres. Better quantification of chemotherapy requirements using data from the National Cancer Registry and resource-sensitive treatment guidelines can help reduce stock outs and facilitate more effective and efficient procurement processes.

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INTRODUCTION

Drug shortages are occurring at an alarming frequency worldwide and represent a complex global issue.[1-7] Pediatric and adult patients with cancer are a vulnerable population adversely affected by drug shortages.[8,9] In high-income countries (HICs), these shortages are primarily the result of a lack of financial incentives for manufacturing and mostly affect inexpensive intravenous injectable or oral generic forms of cancer drugs.[10] Earlier studies have hypothesized that in low- and middle-income countries (LMICs), these shortages are related to weak infrastructure for the procurement and distribution of drugs, which results in erratic availability of drugs and frequent stock outs.[11-13] Although this problem is pervasive in LMICs and it undermines cancer care delivery and the potential for cure, no studies, to our knowledge, have quantified the scope of chemotherapy stock outs in these regions.

Botswana is a middle-income country of 2.2 million people in sub-Saharan Africa.[14] The country's Ministry of Health and Wellness (MOHW) formulates national standards for the delivery of health care. Currently, a decentralized network of clinics and hospitals provides approximately 90% of the population with government-funded health care and essential drugs.[15] The Central Medical Store (CMS) is a semiautonomous public sector entity that is charged with the procurement and distribution of pharmaceuticals and other health care commodities to all government health care facilities, including four cancer centers in Botswana.

The WHO's Essential Medicines List (EML) is an important guide for prioritizing drugs for inclusion in Botswana's National Essential Medicines List (NEML), which is an initial step in achieving access to drugs in LMICs.[16,17] However, inclusion in the NEML does not guarantee that these drugs are actually available to and affordable for patients. In this study, we examined the formulary

of NEML in Botswana and the supply chain of cancer drugs. We also quantified the number and duration of chemotherapy stock outs using CMS national stock data and performed a cost analysis that compared drugs that experience stock out with those that do not.

METHODS

Data Collection

Assessment of the Botswana NEML for cancer was based on the version approved in 2015. The availability and buyer price of cancer drugs was analyzed using data from a weekly stock catalog sent by CMS to all pharmacy departments in government hospitals and the 2015 Central Medical Stores–Drugs, Medical Equipment Management Services, and Non-Drug Products Catalogue. For the purpose of this report, we excluded data on palliative and supportive therapies.

Comparative data from the WHO EML was obtained from "The Selection and Use of Essential Medicines (including the 19th WHO Model List of Essential Medicines and the 5th WHO Model List of Essential Medicines for Children)."[18] Prices were compared between the Botswana buyer price and the median drug buyer price on the global market using the WHO publication "MSH International Drug Price Indicator Guide-2014."[19] The median price ratio was computed as the ratio of the country buyer price to the Management Sciences for Health (MSH) median international price, used here as the international reference price (IRP). This methodology is described by the WHO and Health Access Initiative (HAI). In the public sector, a median price ratio (MPR) of 1 or less is indicative of an efficient procurement process, whereas an MPR below 3 is considered efficient for the private sector.[20]

Interviews

In-person interviews with key informants consisting of a group of four members of the pharmacy team and the head of the oncology department at Princess Marina Hospital (PMH: the major cancer referral center in Gaborone, Botswana) were conducted between October 2015 and January 2016. The interviews took place at the health facility where the interviewees were located. These interviews were unstructured and open-ended, and the purposes were to understand data on the Botswana NEML and to informally explore factors associated with the supply chain of pharmaceuticals in the public sector. This was not a main aim of the study and was purely exploratory to inform future research and implementation.

Statistical Analysis

Descriptive statistics were used to describe the mean and median duration of stock out for drugs listed on the Botswana NEML. Exploratory analyses were performed to assess the association between likelihood of stock out and to estimate the total cost of complete therapy per patient using the regimen for the disease with the highest incidence the drug is indicated for. The analysis was performed using both the median international buyer price for the complete list of cancer drugs on the NEML and the Botswana buyer prices for drugs for which these price data were available. We performed nonparametric analysis using the Wilcoxon rank sum test to determine the difference between cost of therapy per patient for drugs that experienced a stock out versus those that did not. We computed a rank correlation between cost of therapy per patient and duration of stock out to test whether the duration of stock out was related to cost of therapy per patient. Further exploratory analysis used the Wilcoxon rank sum test to determine the difference in median MPR stratified by stock out status. Annual trend of number of chemotherapy drugs stocking out in the course of the year was evaluated by linear regression with Pearson correlation coefficients.

Ethical Review

This study, which used routinely collected programmatic aggregated data, was discussed with and exempted from a review by the Botswana Health Research and Development Committee (HRDC). Requests for programmatic data used were made in accordance with standard request procedures from the national cancer registry at MOHW and the pharmacy department at PMH.

RESULTS

The Botswana NEML

The Botswana national essential drugs for cancer are classified into two categories: the stockable

Table 1. Alignment of WHO EML for Cancer and the 2015 Botswana NEML

Drugs on the WHO EMLs for 2013 and 2015	Drugs on the Botswana NEML	Drugs on the WHO EML but not on the Botswana NEML	New Drugs Added to the WHO EML in 2015	NEML Nonstockable List
All-trans retinoic acid*		X	X	
Aromatase inhibitors (including anastrazole, letrozole, and exemestane)	X		X	X
Asparaginase		X		
Bendamustine	X		X	X
Bicalutamide†	X		X	
Bleomycin	X			
Calcium folinate	X			
Carboplatin	X		X	
Capecitabine	X		X	X
Chlorambucil	X			X
Cisplatin	X		X	
Cyclophosphamide	X			
Cytarabine	X			X
Dacarbazine	X			
Dactinomycin	X			
Daunorubicin		X		
Docetaxel	X			X
Doxorubicin	X			
Etoposide	X			
Fludarabine	X		X	X
Fluorouracil	X			
Granulocyte colony-stimulating factor (including filgrastim, peg-filgrastim, and lenograstim)		X	X	
Gemcitabine	X		X	X
Hydroxycarbamide		X		
Ifosfamide	X			X
Imatinib	X		X	
Irinotecan	X		X	X
Leuprolin class (includes goserelin, triptorelin, leuprolin)	X		X	X
Mercaptopurine		X		
Mesna	X			X
Methotrexate	X			

(Continued on following page)

list and the non-stockable/special request list. Theoretically, CMS maintains a buffer stock of all drugs on the stockable list, whereas those on the nonstockable/special order list require that the prescribing specialist physician place an advance order each time the drugs are needed. The Botswana NEML has 18 of the 25 drugs on the 2013 edition of the WHO EML for cancer and an additional 15 of the 16 from the list of essential medicines added in 2015 (Table 1), for a percentage alignment of 80.5% between the Botswana NEML and WHO EML. The drugs not included in the NEML are primarily used in the treatment of acute leukemia, which is currently not treated in the country and for which patients are referred to South Africa. Additional drugs on the Botswana NEML that are not on the WHO EML are melphalan, mitoxantrone, temozolomide, bortezomib, thalidomide, sorafenib, bevacizumab, and busulfan.

Analysis of Chemotherapy Stock Outs

We measured availability of drugs on the NEML by quantifying the number and duration of stock outs reported by CMS. Figure 1 shows chemotherapy stock outs from January 1 to December 31, 2015. At least 13 of the 33 drugs on the Botswana NEML were out of stock for defined periods of time ranging from 10 days to 211 days. The mean duration for stock outs was 59.8 days, and the median duration for stock outs was 30 days for these 13 drugs. Excluding drugs on the nonstockable/special order NEML list (ie, chlorambucil, capecitabine, and anastrozole), the mean duration of stock outs was 35.9 days, and the median duration of stock outs was 29 days. Figure 2 shows the annual trend of the number of stock outs by month. There was a significant positive correlation between the time of the year and the number of chemotherapy drugs out of stock ($P < .001$), with more stock outs occurring at the end of the 2015 calendar year (Fig 2).

Relationship Between Chemotherapy Costs and Stock Outs

The estimated cost per full dose of treatment for an individual patient using the median international price for a given chemotherapy drug within a therapeutic regimen ranged from $8.38 (US$) for prednisone to $35,669.84 (US$) for trastuzumab. The Wilcoxon rank sum test showed no

Drugs on the WHO EMLs for 2013 and 2015	Drugs on the Botswana NEML	Drugs on the WHO EML but not on the Botswana NEML	New Drugs Added to the WHO EML in 2015	NEML Nonstockable List
Oxaliplatin	X		X	X
Paclitaxel	X			X
Procarbazine		X		
Rituximab	X		X	X
Tamoxifen	X			
Tioguanine		X		
Trastuzumab	X		X	X
Vinblastine	X			
Vincristine	X			
Vinorelbine		X		

Abbreviations: EML, Essential Medicines List; NEML, National Essential Medicines List (for Botswana).
*All-trans retinoic acid (ATRA) also known as tretinoin; capsule/tablet forms only.
†Bicalutamide is a stockable drug that requires an advanced special order from a prescribing physician.

significant difference between cost of therapy per patient for drugs that experienced stock outs compared with those that did not. For cancer drugs that experienced stock outs, rank correlation showed no significant association between cost of full treatment per patient and duration of stock out. Similarly, no significant association was observed between cost and stock outs when the analyses were limited to only the 18 drugs for which Botswana buyer prices were available (MPR analysis was limited to only those 18 drugs; Table 2). The overall median MPR for

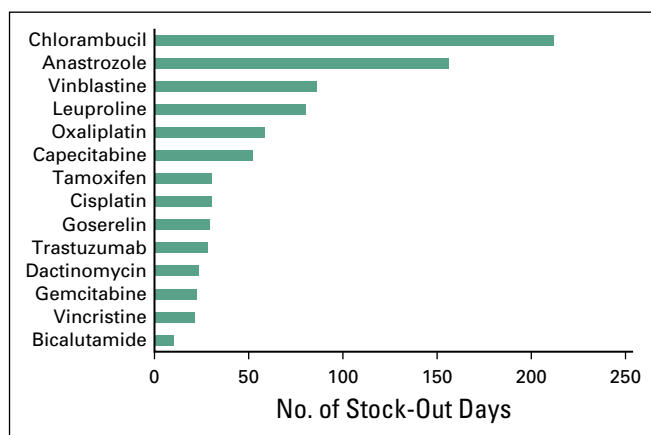the group was 1.145 and the mean was 1.97. For the subset of seven drugs that stocked out on this list, the median and mean MPR were slightly higher at 1.81 and 3.266, respectively, compared with 1.04 and 1.14, respectively, for the 11 drugs that did not experience a stock out. However, nonparametric analysis of the difference in median MPR between the drugs that experienced a stock out versus those that did not was not statistically significant.

Supply Chain of Chemotherapy Drugs

Figure 3 illustrates the supply chain of chemotherapy drugs in Botswana. The MOHW allocates funding for the purchase of all drugs on the NEML. CMS estimates the targets for pharmaceutical coverage on the basis of average monthly consumption data. These data are computed using current demand and ordering patterns from the cancer referral centers. CMS subsequently procures pharmaceuticals from international suppliers to meet these targets. In an exploratory inquiry, the following factors were hypothesized to be associated with stock out of cancer drugs. (1) Funding allocated by the MOHW is inadequate to cover the cost of pharmaceuticals needed for the treatment of cancers diagnosed annually. In addition, the MOHW budget may be subject to delays in releasing funds, which leads to delays in disbursement. (2) In some cases, CMS prices are higher than the median price of drugs on the open market (Table 2). (3) Current forecasts for chemotherapy coverage are populated with average consumption data, which incorporates nonuse of drugs as a result of stock outs. Individual physicians have variable approaches to treating the same disease, physicians come and go all too often, and different physicians have different approaches to treatment. (4) The lack of standardized treatment protocols limits the ability to predict prescribing patterns and forecast the volumetric quantity of drugs needed.

DISCUSSION

Our study is timely in addressing the increasing global burden of stock outs in LMICs. It highlights the importance of evaluating NEML alignment and also rigorously studying the actual availability of essential drugs for cancer treatment within individual health facilities and countries. In this study of the availability of WHO essential
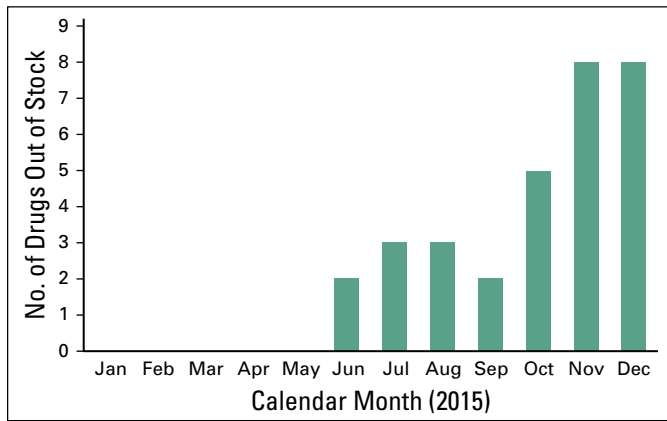

Fig 1. Duration of stock outs in 2015 (days).

Fig 2. Annual trend of stock outs for 2015.

much higher than data reported in the literature from this African region (median alignment of 34.1%) and from HICs (median alignment of 73.2%).[21] These figures attest to the substantial investment in overall health care and efforts to expand access to cancer care made by Botswana's MOHW and its government.

We found that despite the increased alignment of the Botswana NEML with the WHO EML, significant stock outs occurred for chemotherapy drugs used to treat some of the most common cancers diagnosed in Botswana (ie cervical, breast, prostate, and colorectal cancer). The median duration of stock outs was approximately 1 month, implying that for most chemotherapy regimens dosed every 14 or every 21 days, patients were likely to experience suboptimal therapy delivery manifested as delays in therapy, missed doses, or substitution with less efficacious or more costly chemotherapy drugs. On the basis of anecdotal data, we think that similar to NEML alignment, which is one of the highest in the region, the duration of stock outs

medicines for cancer in Botswana, we found that Botswana has an impressively high alignment of 80.5% of its NEML with the most recent WHO EML published in 2015. In June 2016, the updated NEML for Botswana was released after our study had been conducted, and it showed that the Botswana NEML increased in alignment to 85.4% after new drugs were added. This is

Table 2. Comparisons of MOHW Buyer Prices With MSH Median Buyer Prices

Botswana NEML	Quantity and Medium	Method of Administration	Purchasing Unit	MOHW Buyer Price (US$ equivalent)*	Median Reference Price (US$)	Median Price Ratio	Stock Outs
Fluorouracil	50 mg/mL	Injection	10-mL vial	2.87	2.08	1.38	
Bicalutamide	50 mg tablets	Oral	30-tablet pack	146.62	13.29	11.03	X
Bleomycin sulfate	15 IU powder	Injection	Vial	32.60	19.99	1.63	
Carboplatin	450 mg	Injection	Vial	72.10	38.50	1.87	
Chlorambucil	2 mg		25 pack	20.63	32.83	0.63	
Cisplatin	50 mg/50 mL	Injection	50-mL vial	8.62	10.63	0.81	X
Cyclophosphamide	500 mg powder	Injection	Vial	7.64	8.89	0.86	
Cytarabine	100 mg/5 mL	Injection	Vial	22.00	4.31	5.10	X
Dacarbazine	200 mg powder	Injection	Vial	17.32	17.83	0.97	X
Dactinomycin	0.5 mg powder	Injection	Vial	26.07	25.23	1.03	
Doxorubicin	50 mg powder	Injection	Vial	11.36	9.06	1.25	
Etoposide	20 mg/mL	Injection	5-mL vial	4.76	4.57	1.04	
Filgrastim	300 µg/mL (30 million units)	Injection	1-mL vial	51.05	91.37	0.56	
Methotrexate	2.5 mg tablets	Oral	100-tablet pack	10.36	10.40	0.99	
Methotrexate	25 mg/mL	Injection	2-mL ampule	3.31	2.45	1.35	
Tamoxifen	10 mg tablets		30-tablet pack	5.48	2.1	2.61	X
Vinblastine	10 mg	Injection	Vial	20.28	11.23	1.81	X
Vincristine	1 mg powder	Injection	Vial	2.14	4.07	0.53	X

NOTE. Limited to drugs for which cost data are available.

Abbreviations: MSH, Management Sciences for Health; MOHW, Ministry of Health and Wellness (for Botswana); NEML, National Essential Medicines List (for Botswana).

*Exchange rate for January 2014 was $1 to 8.63BWP (Botswana pula).

reported in Botswana is shorter compared with other countries within the region.

One of the supply chain factors related to stock outs was lack of accurate chemotherapy forecasting. The current means of forecasting, which estimates future need on the basis of demand patterns from earlier periods, is flawed because the average monthly consumption is computed over the average of appropriate demand, nonuse due to stock outs, (mis)use of alternative drug regimens due to specific drug stock outs, and differences in physicians' prescribing practices that may not necessarily reflect standard of care. Although demand forecasting is an adequate method in HICs, this method is not ideal in this setting and other LMICs where frequent chemotherapy stock outs occur. Another limitation for procurement of drugs is the lack of standardized treatment guidelines for specific cancers, and thus the inability to predict demand if wide variation exists among practicing oncologists within the country. For instance, in the last 2 years, there has been a turnover of five different oncologists who received their medical oncology training in four different countries. To mitigate the problem of physician turnover, the Botswana MOHW is in the process of developing standardized national treatment guidelines for the treatable cancers that have the highest incidence. Standardized treatment protocols will allow more accurate predictions of specific drug needs by disease and stage. In a subsequent study, we described a methodology for forecasting chemotherapy that uses country-specific incidence data and standardized treatment guidelines to produce volumetric and annual cost estimates of cancer drugs for Botswana.
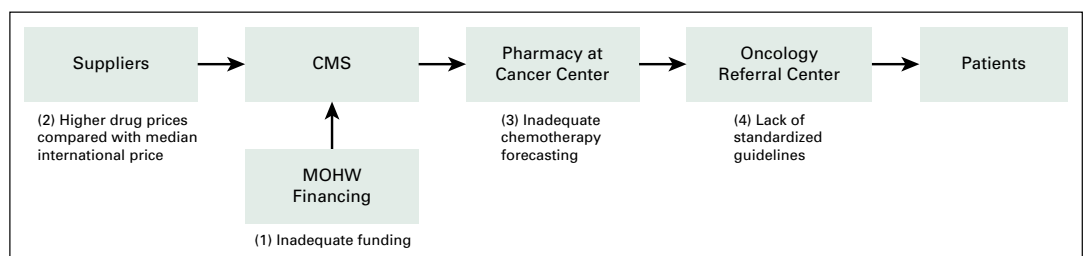
In this analysis, we noted that drugs were significantly more likely to stock out as the calendar year progressed and to peak in the last 3 months. Although this trend is interesting, we were unable to draw any firm conclusions to explain this finding because this pattern of stock out is not aligned with the Botswana government's financial year (which runs from April to March of the following year) and may not be generalizable to other years. Further evaluation, including assessment of stock outs across several years and characterization of procurement details related to tendering processes may be informative.

The chemotherapy pricing market is highly variable and is not transparent for reasons that remain unclear. We estimated that 61% of the 18 drugs with buyer prices had an MPR greater than 1, which may be indicative of inefficient procurement in the public sector. Although our results were not statistically significant, our exploratory analysis showed that drugs that experienced a stock out had higher MPR ratios, suggesting that inefficient procurement leads to a higher likelihood of stock out or vice versa, that is, drugs that experience a stock out are more likely to have inefficient procurement processing as a stopgap measure. This study was not a formal survey of drug prices by the WHO and HAI methodology; therefore, the small number of drugs with available buyer prices does not allow us to make further inferences. The association between MPR and procurement efficiency and its relation to stock outs warrants additional exploration.

The human cost of stock outs of essential drugs for cancer treatment is potentially significant. The efficacy of chemotherapy regimens often depends on delivering the full dose on schedule for a specific number of treatment cycles. For example, in the case of Hodgkin lymphoma, six treatment cycles with four chemotherapy drugs (doxorubicin, bleomycin, vinblastine, and dacarbazine [ABVD]) can be expected to result in a greater than 80% chance of long-term remission. It is likely that administering fewer cycles of therapy, significant delays in cycles of therapy, or the absence of one of the four essential drugs will substantially reduce the potential long-term remission rate, and in some cases,

Fig 3. Schematic of the supply chain of cancer drugs and factors related to stock out. CMS, Central Medical Store; MOHW, Ministry of Health and Wellness (for Botswana).

Suppliers → CMS → Pharmacy at Cancer Center → Oncology Referral Center → Patients

(2) Higher drug prices compared with median international price

MOHW Financing

(1) Inadequate funding

(3) Inadequate chemotherapy forecasting

(4) Lack of standardized guidelines

the curative potential may be reduced to zero. In another example, the vast majority of patients with chronic myeloid leukemia will have long-term disease control with daily administration of the oral tyrosine kinase inhibitor imatinib. It has been well documented that if treatment is interrupted for a significant amount of time, the patient is likely to go out of remission, and remission might not be re-achieved when the medication is reinstituted. In these cases, stock outs can cause needless loss of life.

We recognize that our study has several limitations. The sample size of drugs purchased is small, and consequently we may have missed a cost or MPR association with stock outs. Although we highlight some factors that may be related to stock outs, the scope of a formal analysis of stock outs is outside of the scope of this article, and preliminary data are presented here to inform future research.

In conclusion, to the best of our knowledge, our study is the first to quantify chemotherapy stock outs and related factors in an LMIC. We believe Botswana is an ideal setting for such a study because it has complete stock data, and the MOHW is currently attempting to strengthen the delivery of cancer care by developing national treatment guidelines, among other things. This study begins to address the magnitude of this global issue of potential cancer therapy drug stock outs on the delivery of cancer care and should serve as an impetus for change.

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AUTHORS' DISCLOSURES OF
POTENTIAL CONFLICTS OF INTEREST

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

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