original reports abstract

Substandard Cisplatin Found While Screening the Quality of Anticancer Drugs From Addis Ababa, Ethiopia

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PURPOSE A postmarket evaluation of chemotherapy dosage forms in Ethiopia was conducted to test the accuracy of the chemoPAD, a paper analytical device for drug quality screening.

MATERIALS AND METHODS In September of 2018 in Addis Ababa, Ethiopia, 41 anticancer drug dosage forms (representing 4 active ingredients, 5 brands, and 7 lot numbers) were collected and were rapidly screened for quality using a chemotherapy paper analytical device (chemoPAD). Confirmatory analysis via high performance liquid chromatography was conducted.

RESULTS The chemoPAD showed that the correct active pharmaceutical ingredient was present in doxorubicin, methotrexate, and oxaliplatin injectable dosage forms. However, 11 of 20 cisplatin samples failed the screening test. Confirmatory assay by high-performance liquid chromatography showed that all 20 cisplatin samples—comprising three lot numbers of a product stated to be Cisteen—were substandard, containing on average 54% ± 6% of the stated cisplatin content. Inductively coupled plasma optical emission spectroscopy analysis of five representative samples found 57% to 71% of the platinum that should have been present. The sensitivity of the chemoPAD for detection of falsified products could not be measured (as none were present in these samples), but the selectivity was 100% (no false positives). The sensitivity for detection of substandard products was 55%, and the selectivity was 100% (no false positives).

CONCLUSION Although instrumental analysis by pharmacopeia methods must remain the gold standard for assessing overall drug quality, these methods are time consuming and patients could be exposed to a bad-quality drug while clinical workers wait for testing to be performed. The chemoPAD technology could allow clinicians to check at the point of use for serious problems in the quality of chemotherapy drugs on a weekly or monthly schedule.

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INTRODUCTION

Cancer disproportionately affects patients in low- and middle-income countries (LMICs). In 2020, 70% of newly diagnosed cancer cases will occur in LMICs,[1] where the survival rate for cancers is 30%-50% lower than in high-income countries.[2] Approximately 18.1 million new cancer cases were diagnosed in 2018,[1] and over 20 million new cancer cases are expected annually as early as 2030.[3,4] This corresponds to a 77% increase in cancer incidence[5] and approximately 9.6 million cancer mortalities, on the basis of mortality rates from 2018.[1] In addition to socioeconomic disparities and lack of affordable access to care, this disparity is caused by multiple other issues, including lack of cancer screening, late-stage diagnosis, social stigma, ethnic and cultural barriers, and substandard or falsified medications.

The WHO estimates that 1 in 10 medical products found in LMICs are either substandard or falsified.[6] The toll taken by using substandard or falsified chemotherapy drugs is especially devastating. For other drug classes, such as antibiotics, if the patient's health does not improve, then the quality of the medication may be questioned. In cancer treatment, when progress is poor, the link between drug efficacy and the patient's health status is one of many possible explanations.

There are multiple reasons that a cancer patient's health may decline, even when medications of proper active pharmaceutical ingredient (API) content are used in treatment. Patients could develop cancers that are resistant to treatment by a certain mechanism, requiring use of second- and third-line therapies.[7-9] Cancer metastases can also result in malignancies that are resistant to previous therapies.[7] Because of the complexity and acuity of the disease, and personal health and immunologic status of the patient, the chemotherapy quality is often not suspected to be a problem if the patient's health does not improve. The lack of drug

ASSOCIATED CONTENT

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

How can the quality of chemotherapy drugs be monitored in low-income countries, where there may not be technical capacity for chemical analysis of these products?

Knowledge Generated

A novel device for detecting-low quality drugs, the chemotherapy paper analytical device (chemoPAD), was used to screen tiny portions of doxorubicin, methotrexate, cisplatin, and oxaliplatin at an Ethiopian hospital. The chemoPAD found multiple cisplatin samples that were low in the active ingredient; confirmatory assay showed they had only half of the stated amount of cisplatin.

Relevance

The chemoPAD could be used in a clinical context to quickly check the quality of chemotherapy drugs in low-resource settings.

adverse effects may be the only clue for health practitioners that a chemotherapy drug is not efficacious, although even that is difficult to ascertain because of multiple drugs being used simultaneously.

Several instances of falsified chemotherapy drugs penetrating clinic supply chains have been reported. In January of 2017, in a state-run hospital in Veracruz, Mexico, it was discovered that between 2010 and 2016, 119 patients were treated with a bevacizumab chemotherapy product that may have been falsified.[10] An investigation was launched after Governor Miguel Ángel Yunes announced that patients with cancer had been treated with distilled water under his predecessor's regime. The stated manufacturer, Roche Laboratories, confirmed that 21 vials they were given to examine were falsified and contained no API.[11]

In a later incident, the WHO put out a rapid alert in August of 2017 for falsified bevacizumab and sunitinib that were being circulated in East Africa.[12] These medications were discovered by the National Drug Authority in Uganda and were confirmed to be counterfeit by the manufacturers of the genuine products. In the case of sunitinib, the falsification was blatant; the genuine version comes in a gelatin capsule and the falsified product consisted of blue/gray tablets.

There is little published information about the prevalence of substandard or falsified cancer medications. In 2016, the Pharmaceutical Security Institute ranked oncology drugs as the fifth most commonly falsified drug class.[13] More than 1,500 products have been reported to the WHO Global Surveillance and Monitoring System for substandard and falsified medical products, but $< 6.3\%$ were cancer medicines, and only 19 member states reported in this category.[14] There was no information available about how these drugs were tested or which member states reported them. The Promoting the Quality of Medicines Program (PQM) compiled a report of falsified and substandard medications on the basis of newspaper articles. The PQM report found 11 instances of poor-quality anticancer medications from 9 different countries between 2007 and 2012.[15] The US Pharmacopeia (USP) Medicines Quality Database contains no results for chemotherapy or anticancer drugs.

Currently, no commercial field tests are available for screening chemotherapy drugs at the point of use or even in regulatory laboratories. The Global Pharma Health Fund (GPHF)–Minilab is a valuable screening tool for 90 different pharmaceuticals, including antimalarials, antimicrobials, antituberculosis medications, anthelmintics, antiretrovirals, and cardiovascular drugs.[16] However, the Minilab is not set up to test chemotherapy drugs. Working with chemotherapy drugs comes with unique challenges because of their high toxicity. If a chemotherapy drug is suspected to be substandard, then it will be sent to a laboratory equipped with the necessary safety procedures and instrumentation for confirmatory analysis. The laboratory will generally perform high-performance liquid chromatography (HPLC) to identify and quantify the API present in the medication. This assay is expensive and often takes a considerable amount of time, especially if the sample has to be shipped to another country for analysis.

The chemoPAD is a paper analytical device for rapid field testing of chemotherapy drugs[17] that could be useful to health care practitioners as a screening device for drug quality. Here, we report results from screening chemotherapy drugs with the chemoPAD in a point-of-care setting and document substandard cisplatin collected from two clinics at Black Lion Hospital in Addis Ababa, Ethiopia. Both quantitative and qualitative tests were performed on the suspect product to evaluate the root cause of its low API content.

MATERIALS AND METHODS

Ethics

This study did not involve any human subjects or covert sampling; the main ethical issues were communication protocols with the appropriate regulatory authorities and safe handling of the toxic/carcinogenic chemotherapy

drugs. A standard operating procedure was developed to handle the chemotherapy drugs. The head of the oncology department of Black Lion Hospital and other ward personnel were notified of this research, and ethical approval for the study was obtained through the University of Notre Dame's Institutional Review Board committee (Protocol ID: 15-05-2542, March 21, 2017–March 20, 2018 and 18-02-4442, April 13, 2018–April 12, 2019) and School of Pharmacy, Addis Ababa University Ethical Review Board number ERB/SOP/116/07/2018, dated July 9, 2018.

Methods

Samples were collected in Addis Ababa from the Black Lion Hospital (Tikur Anbessa Specialized Hospital) between September 1, 2018 and September 14, 2018. Samples were screened using the chemoPAD at Black Lion Hospital. The oncology pharmacists/nurses were asked about the step-by-step preparation procedure for injectable chemotherapy agents. They shake the septum-capped vial, remove the calculated amount of dosage form with a syringe, and inject it into an intravenous (IV) bag for patient treatment. They confirmed that the vial contents were never diluted by adding liquid to the vial to rinse it out. The vials were set aside in the preparation area (a laminar flow hood) after patient treatment, and vials with drug leftovers were removed for chemoPAD screening within 72 hours. In most cases, several milliliters of the original solution were left over in the vial. For each sample, approximately a milliliter of the residual solution was transferred to a microcentrifuge tube, and 60 μL was immediately removed for testing on a chemoPAD.[17] The microcentrifuge tubes were sealed with parafilm for transport to the United States, then stored in a refrigerator for up to 2 weeks. Samples were shipped by air in a 48-hour period.

Confirmatory analysis was conducted using HPLC at the University of Notre Dame. Additional testing on Cisteen samples was conducted to measure pH, platinum content through inductively coupled plasma optical emission spectroscopy (ICP-OES), and mass spectrum taken. The experimental details of each process and sample collection details are described fully in the Data Supplement.

RESULTS

Samples

This study was conducted to follow up on earlier results[17] from the development of the chemoPAD device, which suggested that substandard chemotherapy drugs might be present in the Ethiopian supply chain. Over a period of 2 weeks, a total of 41 vials were collected after chemotherapy sessions at the Black Lion Hospital in Addis Ababa, Ethiopia. The medicine for each patient is prepared by withdrawing a calculated dose of chemotherapy agent from the vial for preparation of an IV infusion; in most cases, several drops to several milliliters of the chemotherapy agent are left in the vial. The samples included one vial of methotrexate (25 mg/mL), six vials of oxaliplatin (5 mg/mL), fourteen vials of doxorubicin (2 mg/mL), and twenty vials of a product stated to be cisplatin (1 mg/mL), with the brand name Cisteen.

The cisplatin samples were all stated to be manufactured by Naprod Life Sciences in Andheri, Mumbai, Boisar District-Thane, India, and included three unique lot numbers. All but one of the cisplatin samples listed the same manufacture and expiration dates.

Screening With the chemoPAD

All of the products were screened at the Black Lion Hospital within 72 hours of collection using a chemoPAD. The chemoPAD is an inexpensive paper test card that has previously been demonstrated capable of qualitative testing for methotrexate and doxorubicin and semiquantitative testing of cisplatin and oxaliplatin.[17]

The chemoPAD contains twelve lanes (labeled A-L) predosed with color reagents, a plastic cover, and an absorbent paper strip onto which 60 μL of the injectable drug is placed. The chemoPAD usage is depicted in Figure 1.

Qualitative analysis of methotrexate and doxorubicin was performed, because the chemoPAD is not able to quantify these APIs. The chemoPAD results showed that the correct API was present in all of the samples. Semiquantitative analysis of oxaliplatin and cisplatin was performed and gave concerning results. The chemoPAD includes a color test in lanes C and D in which tin chloride reduces platinum compounds to yellow-colored nanoparticles.[17] The more platinum is present in the sample, the darker the yellow color. On the basis of both visual and ImageJ analysis of the color intensities, the oxaliplatin samples contained the proper amount of platinum. However, there was a lower-than-expected platinum content for the Cisteen samples, many of which gave a faint yellow color or were absent of the expected yellow color (Fig 2). Of the twenty Cisteen samples, nine were flagged as suspicious by visual comparison with a standard image. When ImageJ analysis was used to assess the chemoPAD images, eleven samples were marked as suspicious.

HPLC

The USP monograph standard for satisfactory API content for these four chemotherapy drugs is 90%-110%. HPLC was run on all samples collected of methotrexate, oxaliplatin, and doxorubicin. The methotrexate passed assay at 100.7% API. The oxaliplatin tested passed assay except for one sample, which was slightly higher than the USP recommendations at 113% API. The doxorubicin samples failed marginally, with an average 84.7% API content, as has previously been reported for this brand of doxorubicin.[17] Full details for of the HPLC system suitability and assay results for these three drugs are provided in the Data Supplement.

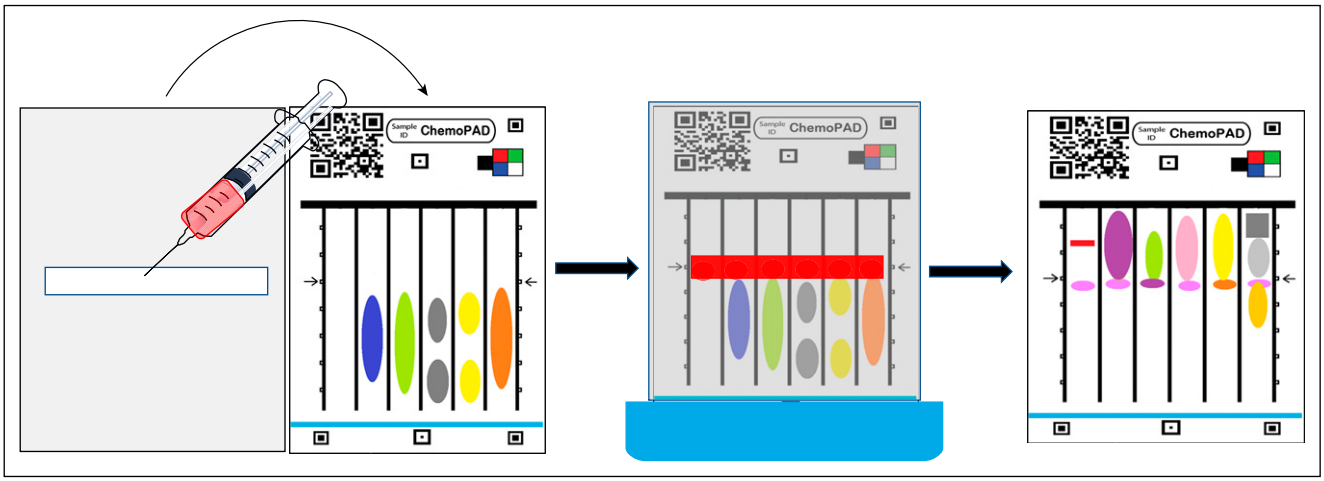

FIG 1. Using the chemoPAD to test chemotherapy drugs. First, approximately 60 μL of drug is deposited onto the sample application area, an absorbent paper strip. The card is then folded, which deposits small spots of the drug from the absorbent paper strip into all twelve of the lanes. The bottom edge of the card is placed in water, which is drawn up the lanes by capillary action. The water dissolves the color reagents stored in the lanes and sweeps them over the spots of drug. The colors that form and the intensities of those colors reveal the presence of functional groups and excipients in the drug.

Of the 20 Cisteen samples tested in Ethiopia, only 14 had sufficient volume remaining for HPLC analysis. Out of these 14 samples, all failed HPLC assay for API content, with an average value of 54% ± 6% API (Table 1). Most of the HPLC chromatograms showed a small shoulder for the aquated species of cisplatin (where water has reacted with the drug) at around 2.5 minutes, typically composing 1%-3% of the integrated peak intensity (Data Supplement). This degradation product is described in the literature.[18] To check whether excipients in the dosage form were interfering with detection of the cisplatin, a spike recovery experiment was performed by adding standard reference cisplatin to a sample of Cisteen. The 92% spike recovery indicates that the injection matrix does not interfere with the HPLC assay.

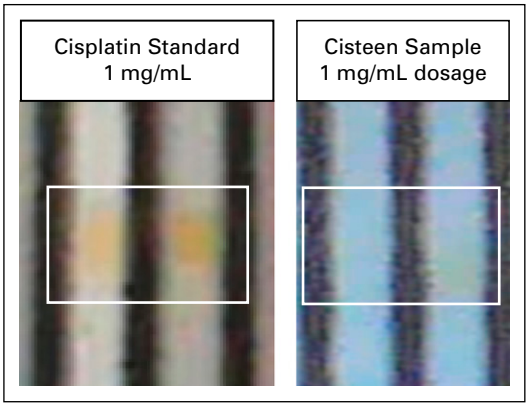

FIG 2. chemoPAD showing cisplatin standard versus Cisteen sample, highlighting the color tests for platinum in lanes C and D. The absence of a strong yellow color in the Cisteen sample indicates a deficient platinum content.

Substandard or Degraded Cisplatin?

The pH of cisplatin should be between 3.5 and 6.2, according to the USP monograph.[19] Higher pH can indicate degradation due to release of ammonia.[20] The pH of five of the Cisteen samples was tested and found to be on the higher end of the range for cisplatin, at pH 6.1 or higher (Data Supplement).

Mass spectroscopy was run on a cisplatin standard and 2 Cisteen samples that had failed assay. The cisplatin sodium adduct $[PtCl_2(NH_3)_2 + Na]^+$ has peaks at 320.9, 321.9,

TABLE 1. HPLC Results From Cisteen Samples

Sample ID, Bottle No.	Lot No.	Manufacture Expiry	API Content, %
1	NN7298A	August 2017-July 2019	38.9
7	NN7298A	August 2017-July 2019	49.7
9	NN7298A	August 2017-July 2019	51.5
11	NN7298A	August 2017-July 2019	53.0
13	NN7298A	August 2017-July 2019	67.1
16	NN7298A	August 2017-July 2019	53.8
19	NN7298A	August 2017-July 2019	56.0
20	NN7298A	August 2017-July 2019	58.4
8	NN6383A	August 2016-July 2018	52.8[a]
5	NN7306A	August 2017-July 2019	59.3
18	NN7306A	August 2017-July 2019	54.7
17	NN7306A	August 2017-July 2019	54.0
15	NN7306A	August 2017-July 2019	53.0
14	NN7306A	August 2017-July 2019	55.4

Abbreviations: API, active pharmaceutical ingredient; HPLC, high-performance liquid chromatography; ID, identifier.

[a]Product expired before analysis.

322.9, 323.9, and 324.9 m/z. These peaks were identified in all samples tested. We did not observe the known trichloro degradation product of cisplatin $[PtCl_3(NH_3)]^+$,[20] although both Cisteen samples contained a product whose isotope ratios and exact mass indicate a formula of $C_2H_9N_3Pt^+$. This formula corresponds to the acetonitrile adduct $[PtCl(NH_3)_2(CH_3CN)]^+$, which could have formed from the monoaquated cisplatin during the liquid chromatography-mass spectrometry experiment.

ICP-OES was used to independently determine the total platinum content. Samples from three lot numbers of Cisteen contained only between 57%-71% of the platinum that should have been present (Table 2). Because degradation of cisplatin cannot destroy the platinum atoms, this result suggests that the proper amount of cisplatin was not put into the products during manufacture.

DISCUSSION

The samples of chemotherapy drugs were collected from residual solution left in the vials after patient treatments and refrigerated before and after transport, only being at room temperature for 48 hours. This could affect the assay results in several ways. For example, evaporation would concentrate the solution and give artificially high assay values, degradation could lower the assay value, and if the pharmacists rinse out the vials during preparation of patient doses, this action could dilute the drug and result in an artificially low assay value. Because of the known thermal instability of doxorubicin in solution,[21] it is possible that the marginal assay results found in this study for doxorubicin are due to degradation during transport. However, we do not believe these hypotheticals are at play for the cisplatin samples. Multiple samples of a product stated to be Cisteen (1 mg/mL cisplatin in saline) were found to contain only 39%-67% of the stated API content. A previous study of cisplatin stability demonstrated that cisplatin in dosage form was stable for up to 30 days at room temperature, protected from light.[22] Although the cisplatin samples show some degradation products, the 2 days at room temperature are not sufficient to account for the degradation of half of the product, and the low platinum content measured by ICP suggests that these samples did not contain the correct quantity of cisplatin to start with. The oncology pharmacists confirmed that during preparation of patient IV injections, the required portion of the drug is removed from the vial but nothing is put into the vial. The other samples of chemotherapy drugs collected at the same time and with the same methods show no indication of dilution or degradation during transportation. For example, 6 samples of oxaliplatin solutions for injection assayed at 106%-113%, and a sample of methotrexate solution for injection assayed at 100%.

TABLE 2. Inductively Coupled Plasma Results for Cisteen Samples Representing Each Lot No.

Sample ID (lot No.)	Pt 265.945 (ppm)	Expected Pt, %
Cisplatin standard	12.8219	100
C15 (NN7306A)	7.7304	60
C14 (NN7306A)	7.6202	59
C20 (NN7298A)	8.1445	63
C16 (NN7298A)	7.3596	57
C8 (NN6383A)	9.2690	72
Blank	0.0011	—

Abbreviations: ID, identifier; ppm, parts per million; Pt, platinum.

This pilot study shows that an inexpensive paper test card can be used in a field setting to identify substandard cisplatin. The sensitivity of the chemoPAD for detection of falsified products could not be measured in this study (because no falsified products were present in these samples), but the selectivity was 100% (no false positives). The sensitivity for detection of substandard products was 55%, and the selectivity was 100% (no false positives). The chemoPAD is meant to be used as a drug screening tool to find poor-quality products to send to confirmatory analysis. It is not a replacement for HPLC testing, as it has limited ability to detect diluted products.

The sampling method was developed for use in medical settings where there are not enough chemotherapy drugs to treat all the patients who need them. The test uses tiny drops of the drug left over from patient treatment, so it is not necessary for the hospital to purchase additional vials or withdraw vials that are needed for patient treatment. The substandard level of cisplatin could have serious clinical consequences, such as failure of treatment. At least 14 patients at Black Lion Specialized Hospital and the chemotherapy health center have been exposed to these risks.

The Ethiopian regulatory authorities were informed about this product in early 2019. On the basis of the analytical results in this study, the regulatory authority of Ethiopia, the Ethiopian Food and Drug Administration Authority, is working to strengthen its capacity on all aspects of the regulatory functions (ie, registration, inspection, quality control, and postmarketing surveillance) for anticancer drugs, with the future aim that loopholes in the system that allowed for substandard and/or falsified products to enter the market will be circumvented.

In conclusion, important steps in closing the gap in cancer outcomes between LMICs and high-income countries include ensuring chemotherapy drug quality along with earlier-stage cancer detection and access to care. The presence of seriously substandard cisplatin in the supply chain is deeply concerning. Until there is a robust global system for postmarket monitoring of chemotherapy drugs, pharmacists must more actively inspect and challenge suspicious-looking drugs, such as in the above case, where

a visual inspection would have shown the same dates of manufacture and expiration dates of several different lots of a product. In addition, health care professionals, other caregivers, and cancer researchers in LMICs must be alert to lack of efficacy, unexpected (or lack of) adverse events or drug interactions, and other unusual patient outcomes that might indicate poor-quality products have penetrated a local supply chain. Where possible, quality assurance measures should be incorporated into the development of supply chains for chemotherapy drugs. In future studies, the results of chemoPAD screening could be used to guide a local response by the pharmacists or other health care professionals prescribing the drugs, such as reporting the suspect product to the drug regulatory agency and meanwhile switching patients to another brand of chemotherapy agent. This would allow the necessary confirmatory analysis process to take place but would also protect patients from exposure to a possible substandard product.

Chemotherapy drugs present special challenges for analysis because of their high toxicity. Although the regulatory authorities in Ethiopia are aware of the results of this study, sustainably regulating the quality of chemotherapy products in this and other LMICs will require developing capacity to routinely assay these products. We urge the global community, the WHO, and local agencies to step up technical assistance for surveillance and analysis of chemotherapy drugs in concert with efforts to increase access to chemotherapy products.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Ferlay J, Colombet M, Soerjomataram I, et al: Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer 144:1941-1953, 2019
2. Farmer P, Frenk J, Knaul FM, et al: Expansion of cancer care and control in countries of low and middle income: A call to action. Lancet 376:1186-1193, 2010
3. Shah SC, Kayamba V, Peek RM Jr, et al: Cancer control in low- and middle-income countries: Is it time to consider screening? J Glob Oncol 10.1200/JGO.18.00200
4. Allemani C, Matsuda T, Di Carlo V, et al: Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): Analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet 391:1023-1075, 2018
5. Bray F, Soerjomataram I: The changing global burden of cancer: Transitions in human development and implications for cancer prevention and control in: Gelband H, Jha P, Sankaranarayanan R, et al (eds): Cancer: Disease Control Priorities, Volume 3 (ed 3). Washington, DC, World Bank, 2015
6. World Health Organization: A study on the public health and socioeconomic impact of substandard and falsified medical products. Geneva, World Health Organization, 2017
7. Luqmani YA: Mechanisms of drug resistance in cancer chemotherapy. Med Princ Pract 14:35-48, 2005 (suppl 1)
8. Huisman C, Smit EF, Giaccone G, et al: Second-line chemotherapy in relapsing or refractory non-small-cell lung cancer: A review. J Clin Oncol 18:3722-3730, 2000
9. Hanna N, Johnson D, Temin S, et al: Systemic therapy for stage IV non-small-cell lung cancer: American Society of Clinical Oncology clinical practice guideline update summary. J Oncol Pract 13:832-837, 2017
10. Mexican Secretary of Health: Results of the investigation of the case of Veracruz. (2017). https://www.gob.mx/salud/prensa/resultado-de-la-investigacion-del-caso-veracruz- 96471?idiom=es
11. Cancer drug probe finds 21 vials of fake products. Mexico News Daily, Feb 23, 2017
12. World Health Organization: Medical Product Alert N° 3/2017: Falsified Avastin (bevacizumab) and Sutent (sunitinib malate) circulating in East Africa. https://www.who.int/medicines/publications/drugalerts/drug_alert3-2017/en/
13. Venhuis BJ, Oostlander AE, Giorgio DD, et al: Oncology drugs in the crosshairs of pharmaceutical crime. Lancet Oncol 19:e209-e217, 2018
14. World Health Organization: WHO Global Surveillance and Monitoring System for substandard and falsified medical products. Geneva, World Health Organization, 2017
15. McGinnis M: Media Reports on Medicine Quality: Focusing on USAID-assisted Countries. Promoting Quality of Medicines Program. Rockville, MD, United States Pharmacopeia, 2013
16. Global Pharma Health Fund: GPHF-Minilab - Fact sheet. https://www.gphf.org/minilab/factsheet.htm
17. Smith M, Ashenef A, Lieberman M: A paper analytical device to monitor the quality of four chemotherapy drugs. J Glob Oncol 10.1200/JGO.18.00198
18. Brandsteterová E, Kiss F, Chovancová V, et al: HPLC analysis of platinum cytostatics. Neoplasma 38:415-424, 1991
19. Anonymous: Cisplatin, in US Pharmacopeia-National Formulary (ed 2), 2017, pp. 3444-3448
20. Zieske PA, Koberda M, Hines JL, et al: Characterization of cisplatin degradation as affected by pH and light. Am J Hosp Pharm 48:1500-1506, 1991
21. Poochikian GK, Cradock JC, Flora KP: Stability of anthracycline antitumor agents in four infusion fluids. Am J Hosp Pharm 38:483-486, 1981
22. Karbownik A, Szałek E, Urjasz H, et al: The physical and chemical stability of cisplatin (Teva) in concentrate and diluted in sodium chloride 0.9%. Contemp Oncol (Pozn) 16:435-439, 2012