Retrospective Analysis of the Dose Banding Technique in a Public Hospital in the Agreste of Pernambuco

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Análise Retrospectiva da Técnica de Banda de Dosagem em Hospital Público do Agreste de Pernambuco

Análisis Retrospectivo de la Técnica de Banda de Dosis en un Hospital Público de la Región Agreste de Pernambuco

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ABSTRACT

Introduction: The dose banding technique standardizes doses of anticancer drugs, rounding them into predefined bands. This approach aims to optimize resources, reduce waste, and ensure safety in the preparation of chemotherapy. Created in the United Kingdom, dose banding allows doses to be prepared more quickly and economically, with controlled variations, increasing the supply of services without increasing costs to the health system. Agreed upon by the multidisciplinary team, this approach facilitates the management of cancer treatment, maintaining its efficacy and safety. **Objective:** Analyze the sample using the dose banding technique in a public hospital located in the Agreste region of Pernambuco. **Method:** To identify the antineoplastics with dose banding most likely to impact the production service of pharmaceutical preparations, three criteria (limit of viability) indicating the possible antineoplastics to be viable products were used to consider the applicability of the technique according to logarithmic dose banding: (a) antineoplastic preparations ≥ 150 per year; (b) individualized doses ≥ 10 per dose banding; (c) total dose bands ≤ 5 covering a total of ≥ 60% of all individualized doses for a given drug. **Results:** A total of nine antineoplastics showed viability according to the study: cyclophosphamide, cisplatin, docetaxel, doxorubicin, fluorouracil-bolus, fluorouracil-pump, gemcitabine, irinotecan, oxaliplatin, and paclitaxel. Carboplatin results were not enough to achieve viability for production through dose banding. **Conclusion:** There is a need for more research on the performance of technologies and processes for the applicability of the dose banding technique.

Key words: Antineoplastic Agents/ administration & dosage; Economics, Pharmaceutical; Hospitals, Public; Pharmaceutical Preparations.

RESUMO

Introdução: A técnica de banda de dosagem padroniza doses de medicamentos anticâncer, arredondando-as em faixas predefinidas. Essa abordagem visa otimizar recursos, reduzir desperdícios e garantir segurança no preparo das quimioterapias. Criada no Reino Unido, a banda de dosagem permite preparar doses de forma mais rápida e econômica, com variações controladas, aumentando a oferta de serviços sem elevar custos ao sistema de saúde. Pactuada entre a equipe multidisciplinar, essa abordagem facilita a gestão do tratamento oncológico, mantendo sua eficácia e segurança. **Objetivo:** Analisar a amostra de acordo com a técnica de banda de dosagem em hospital público do Agreste de Pernambuco. **Método:** Para identificar os antineoplásicos com banda de dosagem mais prováveis de impactar o serviço de produção das preparações farmacêuticas, três critérios (limite de viabilidade) indicando os possíveis antineoplásicos a serem produtos viáveis foram utilizados para considerar a aplicabilidade da técnica conforme banda de dosagem logarítmica: (a) preparações antineoplásicas ≥150 por ano; (b) doses individualizadas ≥10 por banda de dosagem; (c) total de faixas de dose ≤5 que abrange um total ≥60% de todas as doses individualizadas para determinado medicamento. **Resultados:** No total, nove antineoplásicos apresentaram viabilidade de acordo com o estudo: ciclofosfamida, cisplatina, docetaxel, doxorrubicina, fluorouracil-bólus, fluorouracil-bomba, gencitabina, irinotecano, oxaliplatina e paclitaxel. A carboplatina não obteve resultados para atingir viabilidade para produção por banda de dosagem. **Conclusão:** Há necessidade de mais pesquisas sobre performance das tecnologias e processos para aplicabilidade da técnica de banda de dosagem.

Palavras-chave: Antineoplásicos/administração & dosagem; Farmacoeconomia; Hospitais Públicos; Preparações Farmacêuticas.

RESUMEN

Introducción: La técnica de banda de dosis estandariza las dosis de fármacos anticancerígenos, redondeándolas a rangos predefinidos. Este enfoque busca optimizar recursos, reducir el desperdicio y garantizar la seguridad en la preparación de la quimioterapia. Creada en el Reino Unido, la banda de dosis permite preparar las dosis de forma más rápida y económica, con variaciones controladas, lo que aumenta la oferta de servicios sin incrementar los costos para el sistema sanitario. Consensuado por el equipo multidisciplinario, este enfoque facilita la gestión del tratamiento del cáncer, manteniendo su eficacia y seguridad. **Objetivo:** Analizar la muestra según la técnica de bandas de dosis en un hospital público de la región de Agreste, Pernambuco. **Método:** Para identificar los antineoplásicos con bandas de dosis con mayor probabilidad de impactar en el servicio de producción de preparados farmacéuticos, se utilizaron tres criterios (límite de viabilidad) -que indicaban los posibles antineoplásicos para ser productos viables- para considerar la aplicabilidad de la técnica según banda de dosis logarítmica: (a) Preparaciones antineoplásicas ≥ 150 por año; (b) Dosis individualizadas ≥ 10 por banda de dosis; (c) Total del franjas de dosis ≤ 5 que cubre un total ≥ 60% de todas las dosis individualizadas para un medicamento dado. **Resultados:** Un total de nueve antineoplásicos mostraron viabilidad según el estudio: ciclofosfamida, cisplatino, docetaxel, doxorrubicina, fluorouracilo (bolo), fluorouracilo (bomba), gemcitabina, irinotecán, oxaliplatino y paclitaxel. El carboplatino no obtuvo resultados para lograr la viabilidad para la producción por banda de dosis. **Conclusión:** Existe la necesidad de más investigación sobre el desempeño de tecnologías y procesos para la aplicabilidad de la técnica de banda de dosis.

Palabras clave: Antineoplásicos/administração & dosagem; Economía Farmacéutica; Hospitales Públicos; Preparaciones Farmacéuticas .

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INTRODUCTION

Cancer is understood as a pathological state mostly characterized by the uncontrolled cellular division caused by changes in the control mechanisms of the cellular cycle[1]. It is a set of over 100 different diseases understood by society as something frequently associated with the risk of dying[2]. Cancer can appear in any part of the body, and it starts in normal cells that grow as needed. However, damaged cells may grow and multiply uncontrollably, migrating to adjacent tissues, neighboring or distant organs, causing metastases[3,4].

Currently, cancer claims the lives of over 10 million people a year[5]. It is a degenerative disease that affects several life dimensions and causes great financial impact for patients and their families, which can target one out of four people throughout life, being responsible for about 25% of all deaths in adults[6,7]. Estimates predict a leap from 337,000 new cancer cases in 2002 to 704,000 in 2025[8,9]. According to the National Cancer Institute (INCA)[10], from 2023 to 2025, Brazil will have around 2.1 million new cases of the disease. Pernambuco will register approximately 74,000 new cases, and the Agreste, one of the State's subdivisions, will present around 21,000 new cases[11,12].

Cancer treatment involves different modalities such as surgery, radiotherapy, chemotherapy, immunotherapy, targeted therapy, hormone therapy, and bone marrow transplant, all entailing elevated costs. New technologies raise these costs even more, projecting a non-sustainable scenario that threatens access to oncological treatment. Thus, sustainability in access to oncological medication became a global challenge, also affecting developed countries, which face difficulties in ensuring costly treatments for all patients[13]. To promote quality healthcare, cancer preventive and early detection actions are needed, aiming for low-cost treatments, since oncological therapy is very expensive for the National Health System (SUS) and a management challenge for the Ministry of Health[14].

According to Boscato[7], Health Technology Assessment (HTA) aims to obtain maximum benefit with the least expense, promoting rationality based on equity for the use of resources. Thus, Pharmacoeconomics is a science in the health economics field, whose main objective is to apply economic methods to drug therapy. In this sense, dose banding (DB) is a technique that aims to save time and resources in the preparation of chemotherapies and targeted therapies, enabling more services to be offered without financially burdening the healthcare service, agreed upon by all professional team members involved in the oncological pharmacotherapy process[15].

During pharmacotherapeutic treatment, the initial dose depends on specific medication, disease, and patient variables, and it is essential to balance the therapeutic effect and toxicity of antineoplastics[16]. According to Pinkel[17], the dose based on body surface area (BSA) is more adequate for antineoplastic drugs, as there are similarities between BSA doses in animals and humans, in contrast to doses per weight, which vary between species and age. In DB, preparations of antineoplastic drugs are produced with doses rounded up or down to standardize manipulated cytostatic medication doses for use under protocol whenever possible, without negative health results for patients[15].

DB is a system in which oncology professionals, by consensus, adopt standardized values rounded up or down for chemotherapy doses, in predefined bands, replacing the traditional calculation based on BSA. This standardization, based on the logarithmic method described by Zavery and Marsh[15], is applied to the preparation of chemotherapy bags following established protocols[18]. Developed in the United Kingdom in 1998 by Baker and Jones, DB was initially applied to methotrexate and 5-fluorouracil to reduce the waiting time for patients at outpatient clinics. Using BSA ranges of 0.05 m², all patients with BSA between 1.80-1.85 m², for example, received the same dosage (1,125 mg), respecting a maximum variation of 5% concerning the individualized dose[15]. Baker and Jones concluded that DB would allow the preparation of up to 95% of cytostatic mixtures and started to implement the method. This is currently considered a safe system, capable of providing antineoplastic preparations with results comparable to customized manipulation[15,18]. In practice, DB admits an agreed variation of ±5% to 10% between the prescribed dose and the administered dose, agreed upon by the whole team involved[18,19]. Thus, customized doses based on BSA are grouped in predefined dose bands, using the midpoint of the band as reference, to reduce waste and treatment costs[19].

Since its introduction, DB has evolved into two main models: the British, which uses several combined low-dose bags to reach the target dose, and the French, which adopts high-dose bags for single-use per application[15,20]. The British model, created in the United Kingdom and now present in over 50 hospitals, uses low and fixed doses, respecting the threshold of up to three units per dispensation, and for monoclonal antibodies, admits variations of ±5% on the dispensed dose, not exceeding ±10%[15,20,21]. The English National Health Service (NHS) allows a maximum variation of 6% of the prescribed dose and uses volumes compatible with vials to reduce waste[19,22]. Despite being the most adopted and documented, the English model does not have a more complex dispensation, which increases the risk of errors in

outpatient management[15]. Inspired by them, the French model prepares higher standard doses, dispensing only one bag or syringe per prescription, which reduces nursing workload and possible mistakes[15,20]. Pharmacokinetic studies indicate variation of up to 10% between prescribed and dispensed doses, with acceptance of up to 20% in some cases, with no differences between doses based on BSA or banding[15]. The lower complexity of the French model may explain its lower rate of administration errors[15,20].

The objective of this study is to retrospectively analyze the prescribed doses of antineoplastic drugs following the DB technique at a public hospital of the Agreste Region of Pernambuco.

METHOD

Observational study with retrospective analysis of the sample according to the DB technique through a quantitative approach and developed at the chemotherapy center (CQT) of the *Hospital Mestre Vitalino* (HMV). To this end, data on the consumption of all prescriptions containing chemotherapy drugs prepared by the pharmacy team in the hospital's oncology department from July to December 2021 were used.

For inclusion, all prescribed antineoplastics represented in the NHS National DB Table were considered. Regarding exclusion, all pregnant patients and non-compliant prescriptions that presented inconsistent doses and methods of administration were considered. All data was obtained through the MV 2000 software, used by the hospital as a management system. The stock movement and product output reports per patient were analyzed to obtain: the ten most consumed antineoplastics in the preparation of chemotherapy infusions; all prescriptions filled for the ten most consumed antineoplastics; all appointments with at least one prescribed antineoplastic agent; and all prescriptions filled by the CQT pharmacy.

The national NHS DB table, based on the logarithmic method, was used as a reference to define the dose bands for each individualized antineoplastic dose prescribed, using its maximum variation (6%) and respective DB for each customized dose prescribed[14]. This logarithmic scale widely applies to any DB, supporting the application of the standard dose band technique for any chemotherapy drug[18].

To identify the antineoplastics with DB most likely to impact the production service of chemotherapy infusions by the CQT pharmacy team, the products were compared within the DB model. Three criteria (viability limit) indicating the possible antineoplastic drugs to be viable products were used to consider the applicability of the DB technique, as standardized using the logarithmic DB: (a) antineoplastic preparations ≥ 150 per year (≥75 for 6 months); (b) individualized doses ≥ 10 per DB; (c) total dose bands ≤ 5 covering a total of ≥ 60% of all individualized doses for a given drug[15,23].

The necessary number of cycles per year and products per production cycle (batches) was determined through published stability data, dividing the total of weeks per year (52) by the stability in weeks of each analyzed antineoplastic drug. All standard doses would be prepared for a single recipient[18,24].

The number of standard logarithmic DB doses needed to cover 60%, 70%, and 80% of individualized doses of each analyzed drug was also calculated. Finally, the chemotherapeutic agents that presented a maximum of five dose bands, representing a total of 60% of all individualized doses for a given antineoplastic agent, were selected as viable drugs for use in the BD technique[24]. All the data collected was tabulated in the Excel software for later analysis.

The present study did not directly involve human beings; however, it used data from patients' prescriptions. Thus, all the ethical principles ruled by Resolution N. 466/12 of the National Health Council and the data protection law N. 13.709/18 were followed. This study has been approved by the Research Ethics Committee of the *Centro Universitário Tabosa de Almeida (Asces-Unita)*, report number 5.491.567 (CAAE (submission for ethical review): 59240822.0.0000.5203)[25].

RESULTS

A total of 2,646 prescriptions serviced by the CQT pharmacy were analyzed over six months. The prescriptions were composed of 32 different antineoplastic drugs arranged in 41 presentations. Of those, 8 oral route drugs (anastrozole, bicalutamide, capecitabine, cyclophosphamide, chlorambucil, hydroxyurea, letrozole, and tamoxifen), 3 intramuscular or subcutaneous products (fulvestrant, interferon, and triptorelin), and 21 intravenous antineoplastics.

Of the 21 drugs administered via parenteral infusion, 30 distinct pharmaceutical presentations were used (brentuximab vedotin, carboplatin, cyclophosphamide, cisplatin, cytarabine, dacarbazine, docetaxel, doxorubicin, etoposide, fluorouracil, gemcitabine, ifosfamide, irinotecan, oxaliplatin, paclitaxel, pemetrexed, rituximab, trastuzumab, vinblastine, vincristine, and vinorelbine) for the production of 2,923 chemotherapy preparations, composed by 2,675 chemotherapy bags and 248 continuous infusion pumps manipulated by CQT pharmacists.

Based on the data obtained and analyzed from the reports on stock output by patient and stock movements using the MV 2000[26] software, used by the hospital as a management system, it was revealed that 1,996 prescriptions containing at least one oncology product were delivered. Using the MV 2000 search filter, the Product Output Report per Patient was obtained for only the ten most consumed antineoplastic products (presentations) for parenteral use (carboplatin-150 mg/15 ml, cyclophosphamide-1 g, cisplatin-50 mg/50 ml, docetaxel-80 mg, doxorubicin-50 mg, fluorouracil-2.5 g/50 ml, gemcitabine-1 g, irinotecan-100 mg, oxaliplatin-100 mg and paclitaxel-100 mg/16.7 ml) included in a total of 1,490 prescriptions. The quantities of vials used during the period analyzed in the study were also obtained, as described in Table 1. Stability data (weeks), number of cycles per year, and number of chemotherapy preparations produced per cycle of the ten most consumed antineoplastic agents are presented in Table 2[27-32].

The medications with frequency of use of antineoplastic agents ≥ 75 preparations/6 months (≥150 preparations/year) and the number of dosage bands with at least ten prescriptions of individualized doses per band of each chemotherapy agent were obtained and arranged in Table 3.

Of the ten most consumed antineoplastic agents, nine demonstrated the viability of the DB technique. Of those, cytostatic drugs presented five or fewer DB, accounting for 60% of all the individualized doses prescribed. The number of dose bands was also calculated, which included 70%, 80% and 100% of all individualized doses prescribed, as shown in Table 4.

Medications with viable dose bands (≥10) based on the NHS national DB table, which accounted for a total of 60% of all individualized doses prescribed in five dose bands, the variations (in percentage) of doses per DB, and the number of preparations per DB are shown in Table 5. The only antineoplastic agent of the study that did not obtain viability was carboplatin, with 41.95% of individualized doses prescribed in five DB.

DISCUSSION

As a direct consequence of the annual increase in new cases, the financial implications are evident and must be evaluated and managed. According to the study, the American Cancer Society estimates the cost of cancer treatment worldwide will rise from US$290 billion to US$458 billion between 2010-2030. In Brazil, between 1999-2015, the cost of cancer treatment alone leaped from R$470 million to 3.3 billion, seven times more, over 16 years. Two-thirds of these expenses refer only to chemotherapy treatment; however, in Brazil, even with the exponential increase in cancer expenses, investments do not meet needs[33].

Given these challenges, SUS cannot be effective, and despite the public policies for cancer treatment incorporated into SUS, they do not translate to effective rights for each patient. Rights such as access to better medications and services are often violated[34].

This fact demonstrates that the right to integral and universal healthcare is not always respected for cancer patients, partly due to the high complexity of oncological treatments, the number and high cost of antineoplastic drugs, in addition to, in Brazil, a shortage of investments in production and development research of new technologies and medications[35].

When it comes to SUS, the high costs of cancer and its consequences have overwhelmed investments in health. Considering the current indicators of oncological treatment costs, the increase in cancer incidence and funding of innovative and costly technologies provided by SUS (also by legal demands) are important factors in

Table 1. Comparison of pharmaceutical products by concentration, amount of vial, and consumed milligrams

	Medication/presentation	Concentration	Consumed vials	Amount consumed in milligrams
1º	Paclitaxel-100 mg/16.7 ml	6 mg/ml	672	671.4100
2º	Fluorouracil-2.5 g/50 ml	50 mg/ml	442	441.9280
3º	Oxaliplatin-100 mg	5 mg/ml	388	387.6900
4º	Carboplatin-150 mg/15 ml	10 mg/ml	311	310.2404
5º	Gemcitabine-1 g	38 mg/ml	256	255.4930
6º	Irinotecan-100 mg	20 mg/ml	256	255.3400
7º	Doxorubicin-50 mg	2 mg/ml	240	239.2400
8º	Docetaxel-80 mg	20 mg/ml	182	180.8875
9º	Cisplatin-50 mg/50 ml	1 mg/ml	154	153.4200
10º	Cyclophosphamide-1 g	20 mg/ml	151	150.1750

Table 2. Comparison of manipulated pharmaceutical products according to the dose banding model, per the number of prescriptions within viable dose bands

Medication/route of administration	Number of times prescribed (%)	Stability (in weeks)[27-32]	Production Cycles/year	Viable number of dose bands (n. ≥ 10)	Prescriptions in viable dose (%)	Number of products per production cycle
Paclitaxel	464 (23.2%)	4[27,28]	13	11	412 (88.74%)	32
Fluorouracil (bolus)	312 (15.6%)	16[29,30]	4	10	300 (96.10%)	75
Fluorouracil (pump)	248 (12.4%)	16[29]	4	8	243 (97.95%)	61
Oxaliplatin	292 (14.6%)	12[31]	5	11	277 (94.80%)	56
Carboplatin	324 (16.2%)	12[31]	5	15	280 (86.34%)	56
Gemcitabine	177 (8.8%)	12[31]	5	7	173 (97.69%)	35
Irinotecan	85 (4.2%)	12[31]	5	6	75 (88.23%)	15
Doxorubicin	149 (7.4%)	17[32]	4	4	101 (67.77%)	26
Docetaxel	166 (8.3%)	8[32]	7	7	144 (86.70%)	21
Cisplatin	144 (7.2%)	4[31]	13	6	103 (71.50%)	8
Cyclophosphamide	144 (7.2%)	4[32]	13	5	121 (83.43%)	10

Table 3. Comparison of pharmaceutical products by number of individualized doses prescribed ≥10 by DB (viability threshold), coverage number (60%, 70%, 80%, and 100%), and number of prescriptions ≥150 per year (viability threshold)

Medication/route of administration	Individualized doses prescribed (with n. ≥10 individualized doses per DB) (%)	Individualized doses prescribed (80% of coverage)	Individualized doses prescribed (70% coverage)	Individualized doses prescribed (60% of coverage)	Prescriptions ≥ 75 in 6 months (≥150 per year)
Carboplatin	280 (86.34%)	260 (80.18%)	237 (73.09%)	136 (41.95%)	324
Cyclophosphamide	121 (83.43%)	121 (83.43%)	110 (75.85%)	94 (64.82%)	145
Cisplatin	103 (71.50%)	121 (84.00%)	103 (71.50%)	93 (64.56%)	144
Docetaxel	144 (86.70%)	144 (86.70%)	120 (72.26%)	105 (63.23%)	166
Doxorubicin	101 (67.77%)	123 (82.51%)	109 (73.13%)	101 (67.77%)	149
Fluorouracil (bolus)	300 (96.10%)	262 (83.94%)	241 (77.21%)	216 (69.20%)	312
Fluorouracil (pump)	243 (97.95%)	213 (85.86%)	174 (70.14%)	174 (70.14%)	248
Gemcitabine	173 (97.695)	160 (90.35%)	140 (79.06%)	114 (64.38%)	177
Irinotecan	75 (88.21%)	75 (88.21%)	65 (76.45%)	54 (63.51%)	85
Oxaliplatin	277 (94.80%)	245 (83.86%)	214 (73.26%)	193 (66.07%)	292
Paclitaxel	412 (88.74%)	375 (80.78%)	334 (71.95%)	306 (65.92%)	464

Captions: DB = dose banding; ■ = medications that met the DB viability parameters.

the elevation of these costs. Moreover, most investments are also directed at palliative therapy, an advanced state of the disease in which the chances of cure are remote.

Over the last decade, dose banding was widely implemented and interconnected with the NHS clinical practice to service 90% of all chemotherapy prescriptions through the DB system until March 2018. However, in other places, there has not yet been any effectiveness, or the initiatives are still unassertive[18,19].

Research on the stability of antineoplastic agents is an area that draws much attention and is continuously gaining interest. An international study showed that original brand and generic brand medications may differ. Most generic drugs have short expiration dates (approximately 24 hours) due to microbiological reasons, regardless of the actual physical-chemical stability value, in addition to exposing inconsistent physical-chemical stability data on the product information sheets (reconstituted or diluted), presenting different information from one country to another. Although there is no widely accepted methodology for DB, the logarithmic strategy presents advantages for structuring

Table 4. Comparison of pharmaceutical products by the number of different DB at 60%, 70%, 80%, and 100% coverage for individualized prescriptions, number ≥10 individualized doses prescribed by DB, and total number of DB that account for the number ≥60% of all individualized doses

Medication/route of administration	Number of Different DB (100% of coverage)	Number of different DB (with n. ≥10 individualized doses prescribed by DB)	Number of different DB (80% of coverage)	Number of different DB (70% coverage)	Number of different DB (60% of coverage)	Total DB ≥60% of individualized doses prescribed (viability threshold: n. ≤5 DB)
Carboplatin	25	15 (86.34%)	13 (80.18%)	11 (73.09%)	9 (64.15%)	5 (41.95%)
Cyclophosphamide	11	5 (83.43%)	5 (83.43%)	4 (75.85%)	3 (64.82%)	3 (64.82%)
Cisplatin	15	6 (71.50%)	8 (84.00%)	6 (71.50%)	5 (64.56%)	5 (64.56%)
Docetaxel	12	7 (86.70%)	7 (86.70%)	5 (72.26%)	4 (63.23%)	4 (63.23%)
Doxorubicin	15	4 (67.77%)	7 (82.51%)	5 (73.13%)	4 (67.77%)	4 (67.77%)
Fluorouracil (bolus)	13	10 (96.10%)	7 (83.94%)	6 (77.21%)	5 (69.20%)	5 (69.20%)
Fluorouracil (pump)	10	8 (97.95%)	6 (85.86%)	4 (70.14%)	4 (70.14%)	4 (70.14%)
Gemcitabine	9	7 (97.69%)	6 (90.35%)	5 (79.06%)	4 (64.38%)	4 (64.38%)
Irinotecan	13	6 (88.21%)	6 (88.21%)	5 (76.45%)	4 (63.51%)	4 (63.51%)
Oxaliplatin	16	11 (94.80%)	8 (83.86%)	6 (73.26%)	5 (66.07%)	5 (66.07%)
Paclitaxel	21	11 (88.74%)	8 (80.78%)	6 (71.95%)	5 (65.92%)	5 (65.92%)

Captions: DB = dose banding; = medications that met the DB viability parameters; = medications that did not meet the DB viability parameters.

Table 5. Comparison of pharmaceutical products by doses (mg) of the five greatest DB, band range, variations of DB bands in percentage (%), and total number of preparations by DB

Medication/ route of administration	Standard doses and threshold doses									
Carboplatin	Dose (mg)	120		150		180		200		220	
	Band range (mg)	(114.89-124.89)		(144.91-154.91)		(169.71-189.73)		(189.74-209.75)		(209.76-229.77)	
	Variation (%)	Below	Above	Below	Above	Below	Above	Below	Above	Below	Above
		4	-4	4	-3	6	-5	5	-5	5	-4
	Preparations	24 (7.40%)		27 (8.33%)		40 (12.34%)		24 (7.40%)		21 (6.48%)	
Cyclophosphamide	Dose (mg)	480		720		900		1000		1260	
	Band range (mg)	(459.56-509.11)		(689.34-758.93)		(848.52-948.67)		(948.68-1058.29)		(1187.94-1328.15)	
	Variation (%)	Below	Above	Below	Above	Below	Above	Below	Above	Below	Above
		4	-6	4	-5	6	-5	5	-6	6	-5
	Preparations	16 (11.03%)		11 (7.58%)		23 (15.86%)		48 (33.10%)		23 (15.86%)	
Cisplatin	Dose (mg)	40		45		56		63		70	
	Band range (mg)	(37.95-42.42)		(42.43-47.42)		(52.92-59.39)		(59.40-66.40)		(66.41-74.35)	
	Variation (%)	Below	Above	Below	Above	Below	Above	Below	Above	Below	Above
		5	-6	6	-5	6	-6	6	-5	5	-6
	Preparations	33 (22.91%)		18 (12.50%)		11 (7.63%)		16 (11.11%)		15 (10.41%)	
Docetaxel	Dose (mg)	72		80		96		120		132	
	Band range (mg)	(69.98-75.89)		(75.90-83.89)		(91.92-101.81)		(113.84-125.85)		(125.86-139.77)	
	Variation (%)	Below	Above	Below	Above	Below	Above	Below	Above	Below	Above
		3	-5	5	-5	4	-6	5	-5	5	-6
	Preparations	15 (9.03%)		21 (12.65%)		37 (22.28%)		29 (17.46%)		18 (10.84%)	

To be continued

Table 5. Continuation

Medication/ route of administration		Standard doses and threshold doses									
Doxorubicin	Dose (mg)	40		48		80		90		100	
	Band range (mg)	(37.95-41.94)		(45.96-50.90)		(75.89-84.84)		(84.85-94.86)		(94.87-105.82)	
	Variation (%)	Below	Above	Below	Above	Below	Above	Below	Above	Below	Above
		5	-5	4	-6	5	-6	6	-5	5	-6
	Preparations	12 (8.05%)		13 (8.72%)		8 (5.36%)		39 (26.17%)		37 (24.83%)	
Fluorouracil (bolus)	Dose (mg)	500		600		650		700		750	
	Band range (mg)	(474.35-524.39)		(574.45-624.49)		(624.50-674.54)		(674.55-724.54)		(724.55-774.59)	
	Variation (%)	Below	Above	Below	Above	Below	Above	Below	Above	Below	Above
		5	-5	4	-4	4	-4	4	-3	4	-3
	Preparations	30 (9.61%)		51 (16.34%)		38 (12.17%)		50 (16.02%)		47 (15.06%)	
Fluorouracil (pump)	Dose (mg)	2500		3150		3500		3950		4450	
	Band range (mg)	(2371.70-2645.74)		(2969.85-3320.39)		(3320.40-3718.19)		(3718.20-4192.54)		(4192.55-4716.99)	
	Variation (%)	Below	Above	Below	Above	Below	Above	Below	Above	Below	Above
		5	-6	6	-5	5	-6	6	-6	6	-6
	Preparations	22 (8.87%)		39 (15.72%)		59 (23.79%)		34 (13.70%)		42 (16.93%)	
Gemcitabine	Dose (mg)	912		1140		1254		1520		1710	
	Band range (mg)	(873.16-967.32)		(1081.48-1195.62)		(1195.63-1309.74)		(1441.99-1612.18)		(1612.19-1802.48)	
	Variation (%)	Below	Above	Below	Above	Below	Above	Below	Above	Below	Above
		4	-6	5	-5	5	-4	5	-6	6	-5
	Preparations	28 (15.81%)		26 (14.68%)		27 (15.25%)		32 (18.07%)		27 (15.25%)	
Irinotecan	Dose (mg)	180		270		300		330		360	
	Band range (mg)	(171.81-189.73)		(254.56-284.60)		(284.61-314.63)		(314.64-344.66)		(344.67-379.46)	
	Variation (%)	Below	Above	Below	Above	Below	Above	Below	Above	Below	Above
		5	-5	6	-5	5	-5	5	-4	4	-5
	Preparations	15 (17.64%)		11 (12.94%)		13 (15.29%)		14 (16.47%)		12 (14.11%)	
Oxaliplatin	Dose (mg)	100		120		135		150		200	
	Band range (mg)	(94.87-104.87)		(114.89-127.27)		(127.28-142.29)		(142.30-157.31)		(189.74-212.12)	
	Variation (%)	Below	Above	Below	Above	Below	Above	Below	Above	Below	Above
		5	-5	4	-6	6	-5	5	-5	5	-6
	Preparations	52 (17.80%)		34 (11.64%)		50 (17.12%)		26 (8.90%)		31 (10.61%)	
Paclitaxel	Dose (mg)	96		120		132		144		270	
	Band range (mg)	(92.95-101.82)		(113.84-125.85)		(125.86-137.86)		(137.87-152.73)		(254.56-284.59)	
	Variation (%)	Below	Above	Below	Above	Below	Above	Below	Above	Below	Above
		3	-6	5	-5	5	-4	4	-6	6	-5
	Preparations	43 (9.26%)		91 (19.61%)		106 (22.84%)		30 (6.46%)		36 (7.75%)	

Captions: DB = dose banding; = medications that met the DB viability parameters; = medications that did not meet the DB viability parameters.

the DB system: ease of implementation in information systems; proportional constancy; and universal application[24].

A study on the application of DB for the production of antineoplastic agents presented three factors that can determine the viability of production of cytostatic dose bands: a) stability of preparation after dilution; b) frequency of prescription; c) precise number of bands, consolidating the viability thresholds adopted in this analysis[15].

To implement DB, a determining factor is the physical-chemical stability of preparations and assurance of a product with aseptic quality. That way, the stability data obtained illustrate the ability of ensuring a longer lifespan of manipulated parenteral chemotherapeutic products through best practices associated with the preparation of antineoplastic agents, but also through the inclusion of technologies that initially cause potential costs for implementation in the system, such as: polyolefin bags (POF), polyvinyl chloride bags (PVC), glass packaging, polypropylene syringes for packaging prepared batches, in addition to a closed system for handling cytotoxic agents, to ensure the physical-chemical and microbiological stability of the preparations in the DB system[15,23,31,32].

Of the ten most commonly used antineoplastic drugs, only one did not meet at least one of the three determined viability thresholds. Carboplatin did not meet the minimum five DB, which accounts for 60% of the total individualized doses prepared at CQT. That way, carboplatin was the product whose viability for using the DB technique was not met.

Finally, the antineoplastics that met all viability thresholds of this study were cyclophosphamide, cisplatin, docetaxel, doxorubicin, fluorouracil-bolus, fluorouracil-pump, gemcitabine, irinotecan, oxaliplatin, and paclitaxel. That way, a total of nine antineoplastic agents were viable for using the DB technique according to this study.

According to the NHS North of England Cancer Network guidelines, the following cytostatic medications meet the necessary criteria for use in the DB system: cyclophosphamide, doxorubicin, fluorouracil, gemcitabine, and oxaliplatin, corroborating the obtained results[15].

In contrast, according to the expenditure study that used 17 antineoplastic agents (carboplatin; cyclophosphamide; cisplatin; doxorubicin; epirubicin; gemcitabine; irinotecan; paclitaxel; pemetrexed; rituximab), according to which the NHS national DB tables were implemented in the prescription system, after inputting the dose standardization, economical results with reduction of £ 100,000 a month were met in 2016/2017. Even with an increase in prescriptions, there was also a reduction in the internal chemotherapy drug manipulation work, which represented 60% of the total workload/year and decreased to 51% after DB was implemented[36].

According to research that compared five antineoplastic drugs (busulfan; carboplatin; cyclophosphamide; dactinomycin; etoposide) regarding variation between DB doses and individualized prescribed doses, pharmacokinetic analyses results showed no significant differences between individual prescription doses and those obtained with DB, supporting the use of NHS DB tables and indicating that relatively small changes to antineoplastic doses are widely overcome by the variability in exposure and depuration in patients[21].

Similar results were found in a 2012 study by Chatelut et al.[37], with six antineoplastic drugs (cisplatin; docetaxel; doxorubicin; irinotecan; paclitaxel; topotecan) in which there is comparison between standardized DB doses and BSA-based doses through pharmacokinetic criteria presented results that ensured the safety of DB implementation by demonstrating it would not increase patients' plasmatic concentration.

The introduction of the DB technique has the potential to optimize pharmacy aseptic ability, dose rationalization, flexible relocation of standard-doses into bands, reduce expenditures on medications, improve work conditions, reorganize waste management and containment, promote economic advantages to the health-promoting units, and not cause any harm that may compromise the efficacy of the pharmacological treatment delivered to the patient[18,37-40].

CONCLUSION

It becomes evident that implementing the dose banding technique may contribute to rationalizing production and benefiting chemotherapy units, increasing production capacity, decreasing work hours, and promoting efficiency in the antineoplastic manipulation process. However, it is also evident that, in the specific case of successfully implementing DB, it is necessary to make investments in educational processes and technologies that ensure pharmacological quality. Moreover, the practicality of implementing the DB technique must be ensured, as well as the physical-chemical and microbiological control of drugs, to ensure the quality and effectiveness of prepared chemotherapies, without posing any harm to the oncological patient treatment. Finally, it must be highlighted a need for

further research and consensus on the performance of technologies and processes for the applicability of the DB technique.

CONTRIBUTIONS

All the authors have substantially contributed to the study design, planning, data collection, analysis, and interpretation, wording, and critical review. They approved the final version for publication.

DECLARATION OF CONFLICT OF INTERESTS

There is no conflict of interest to declare.

DATA AVAILABILITY STATEMENT

All the contents associated with the article are included in the manuscript, except for the data collected from electronic medical prescriptions obtained through research on the MV2000 database software (management system used by the *Hospital Mestre Vitalino* – Caruaru-PE), which, for containing personal information of patients, are protected by the Personal Data Protection Law (LGPD), N. 13.709/2018.

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