High Priced Medicines: Economic Impact of Two Supply Models (Traditional vs "Dose Banding")

Gustavo H. Marin
Universidad Nacional de La Plata – CONICET

Jose M. Sanguinetti
Laboratorio Integrador de Soluciones Pharma

Sebastian Alvarez
Laboratorio Integrador de Soluciones Pharma

Federico N. Cisneros
Instituto de Obra Social de las Fuerzas Armadas
Hospital Municipal de Oncología Marie Curie

Purpose: High priced medicines (HPM) represent an increasing burden for health system financing. To reduce expenses related to HPM, certain strategies like limiting the funding to therapeutic protocols with the best benefit/risk ratio failed. One of the consequences of limiting funding is lawsuits litigation. This scenario forces health service providers and financiers to explore new options to optimize the investment. Among these solutions, dose standardization also called "dose banding" (DB) showed to be effective and efficient improving access to cancer treatment and diminishing expenses.
The objective of this study is to compare the costs associated to "dose banding" HPM versus with conventional dosage in a developing country such as Argentina.
Materials & Methods: A simulation retrospective study was carried out to analyze the costs associated to the 10 most HPM demanded. A comparison between conventional dosage and "dose banding" were done analyzing data from a compounding company (Lispharma ®). Period of the study: 01-01-2019 to 31-12-2022.
Results: 93,529 doses were analyzed, 34.85% corresponded to the selected HPM provided by conventional method and destined to patients receiving medical care in 66 private institutions of Buenos Aires region. Comparative analysis demonstrated that dose-banding DB was associated with a saving rate of 15.8%.
Conclusion: Dose-banding is a valuable strategy to reduce costs and improve access to HPM.

Keywords: dose-banding, high-priced medicines, cost, health, financers

INTRODUCCION

High priced/high-cost medicines (HPM/HCM) represent an increasing burden for health system financing [1]. A recent study carried out by our group showed that, in Argentina's social security, 21.9% of the expenses are used to finance HPM, benefiting only 1.9% of the insured population [2].

The exponential increasing of prices, the debate about efficacy and the litigation (consequence of limiting funding) are problems related to these drugs that affects either low, middle and high -income countries.

Numerous strategies have been identified to promote the rational use of HPMs, considering their efficacy, safety, pharmacoeconomic, and their impact on public health. Limiting funding to certain therapeutic protocols based on the best clinical benefits was one of them. Despite this type of measures, coverage requests and lawsuits increase, forcing health providers to explore new alternatives.

Among these solutions, dose standardization of HPM/HCM (also called "dose banding") [3], has been tested based on using a "rounded" doses (optimizing commercial presentations of drugs), avoiding wasting of medications and outsourcing compounding. [4,5,6,7].

Almost two thirds of HPM are treatments for cancer or autoimmune diseases. Cytostatic and biological agents are traditionally dosed using anthropometric parameters as body surface area generating differences between the amount present in the commercial formulation of the drug (package, ampoule, bottle) and the prescribed dose [4].

In some situations, a prescribed dose to a patient requires the use of commercial presentations that exceed the dose required. The consequence of the difference between prescription and commercial presentation can result in a waste of drugs and significant expenses in HPM cases.

Dose banding is based on three principles. The first one is a consensus between prescribers and pharmacists who establish dose intervals based on individual calculations for each patient that are rounded in a "band" (allowing a variation from the prescribed doses of ±5% for cytostatic and ±10% for biological agents). This respects the prescribed dose with a small variation without impact in clinical effectiveness [8]. The second principle is that once the dose is prepared, drugs should have a prolonged stability. The third is to have an annual number of prescribed doses for each drug that can result in the appropriate use of wastes. Usually is necessary to outsource the preparation of doses.

Several authors demonstrated that this form of administration of high-priced medicines reduce up to ten percent of expenditure [5] due the use of wastes and diminishing dose cancellation (that can represent the 13% of doses) [2]. On the other hand, dose banding reduces the burden of hospital pharmacy services and shorten the time between the indication and start of treatment. In resume, "dose banding" makes spending more efficient and improves treatment accessibility [1].

Unfortunately, most of this evidence is from high income countries making extrapolation to low-income countries difficult.

The objective of this study was to compare the costs associated to high priced medicine administration by conventional dosage versus "dose banding" in a developing country such as Argentina.

MATERIALS AND METHODS

A retrospective study was carried out analyzing the costs associated to HPC provided by conventional dosage compared with a simulation of identical treatments for those same patients using a dose banding method.

The data was extracted from Lis Pharma® records (a compounding company) which is a health provider of intravenous mixtures of HPM. The period analyzed was from January 1, 2019, to December 31, 2022.

The drugs included in the study are listed in Table 1. These drugs were selected based on the annual number of mixtures performed, the cost (focused on HPM) and the feasibility of applying the "dose banding" system based on the National Health System of England (NHS) data (NHS, 2019) [8]

TABLE 1
LIST OF HPM ANALYZED

bevacizumab
cabazitaxel
cetuximab
docetaxel
nivolumab
paclitaxel
pembrolizumab
rituximab
trastuzumab
trastuzumab+emtasine

The variables selected were: number of patients, number of doses performed, average dose per patient, commercial presentations of the drugs, cost per milligram in pesos (local currency) (prices extract from the official Argentine Pharmaceutical Manual on March 9, 2023) and in United States dollars (at the official dollar rate of the National Bank of Argentina on the same date - $206.75-), dose cost in the conventional dosage (this is the total milligrams of the commercial presentations necessary to cover the prescribed dose) and dose cost under the dose banding system (cost of prescribed milligrams).

For each HPM, the dose band (according to NHS standardization) with the highest rate of use was selected to analyze the following items:

- Percentage of doses that would be feasible to use dose banding
- Price per milligram of the drug
- Price of each dose according to the mode of provision (conventional versus dose banding)
- Nominal price (in Argentine pesos and US dollars)
- Percentage of savings using dose banding per dose and per complete treatment

Statistical analysis: DoseBAND or DoseFIXED data was compared using paired Student's t-tests.

Ethical aspects: the database was coded before analysis to blind the personal data of the patients enrolled in the study. The study protocol was accepted by the HMC- COD110-23 Ethical Committee.

Conflict of Interest: Authors declare no conflict of interest.

RESULTS

During the period of the study (2019-2022), 93,529 doses were prepared at Lispharma ®. From them, 34.85% (n= 32,603) corresponded to the selected drugs (Table 2). These doses corresponded to patients receiving medical care in 66 private institutions of Buenos Aires region.

TABLE 2
NUMBER OF DOSES PER DRUG

Drug	N
Bevacizumab	3247
Cabazitaxel	78
Cetuximab	623
Docetaxel	2012
Nivolumab	1868
Paclitaxel	5782

Pembrolizumab	2737
Rituximab	4980
Trastuzumab	1533
Trastuzumab+emtasine	273

Analyzing *bevacizumab*, 3,247 doses were used for 508 patients (6 doses per patient). In 52% (n=1679) of the doses prepared, an optimization system such as dose-banding could have been used. Due to the frequency of use and the possibility of dose optimization, the 450 mg dose range (118 mixes) was selected. Table 3 gives details of the costs of the different modalities, the nominal and percentage savings per dose by applying dose banding, and the projection to all the average doses per patient registered.

In relation to *cabazitaxel*, twenty patients received this drug representing 78 doses (4 average doses per patient). In all the cases, a dose banding standardization could have been used. Due to the frequency of use and the possibility of dose optimization, the 45 mg dose was selected for the simulation (30 preparations). Table 3 details the costs and savings.

Regarding cetuximab, 623 doses were mixed for 75 patients (8 per patient). In 39% (n=240) of the doses dose banding could have been used. Due to the frequency of use and the possibility of optimization, the 450 mg dose was selected for the simulation (Table 3).

In the case of docetaxel, although it does not have as high a cost as the rest of the HPM selected for this study, the number of protocols and pathologies in which it is used, make it a medicine of special interest to funders. Two thousand and twelve doses were prepared and used in 556 patients (4 doses per patient). The 63% (n=1275) of the doses prepared could be candidate to dose banding. The results of simulation for the more frequent dose (150 mg) are shown in Table 3.

For nivolumab, 1868 doses were split for 237 patients (8 per patient). In 13% (n=245) of the doses could have been used dose banding; 70 mg was the dose selected for the simulation. Table 3 details the costs of the different modalities.

For paclitaxel, 5782 doses were used in 1059 patients (5 per patient). In 42% (n=2448) of cases a dose banding system could have been used. Due to the frequency of use and the possibility of dose optimization, the 140 mg dose was selected for the simulation (Table 3).

For pembrolizumab, 2737 doses and 380 patients (7 per patient). In 0.1% (n=2) of the mixes an optimization system such as dose banding could have been used. The dose optimization used was 240 mg dose (Table 3).

In the case of rituximab, 4980 doses were prepared for 508 patients (10 per patient). Dose banding could have been useful in 20% (n=1010) at an optimization dose of 750 mg.

For trastuzumab, 1533 doses were prepared for 204 patients (8 per patient). Due to the frequency of use and the possibility of dose optimization, the 600 mg dose range (196 preparations) was selected (Table 3).

Finally, for trastuzumab+emtasine, 273 doses were prepared for 27 patients (10 per patient). Due to the frequency of use and the possibility of dose optimization, the 180 mg dose range (72 fractionations) was selected for simulation (Table 3).

The cumulative savings in our sample of HPM were 15.8% (U$S 67503,46).

TABLE 3
COSTS AND SAVINGS OF DOSE-BANDING

Variable	Bevacizumab 450 mg	Cabacitaxel 45 mg	Cetuximab 450 mg	Docetaxel 150 mg	Nivolumab 70 mg	Paclitaxel 140 mg	Pembrolizumab 240 mg	Rituximab 750 mg	Trastuzumab 750 mg	Trastuzumab + Emtasine 180 mg
Cost per mg	$1,539.57	$ 24,158.50	$ 8,612.32	$ 1,933.49	$ 6,688.48	$ 1,038.09	$ 11,727.63	$1,690.72	$ 1,068.36	$ 8,290.28
Cost conventional dose	$ 769,785	$ 1,449,510	$ 3,961,667	$ 309,358	$ 535,062	$ 155,713	$ 3,518,289	$ 1,352,578	$ 940,157.88	$ 1,658,057
Cost dose-banding dose	$ 679,467	$ 1,062,974	$ 3,875,395	$ 286,156	$ 454,816	$ 142,141	$ 2,931,907	$ 986,255	$ 628,196.40	$ 1,492,251
Saving per dose local currency	$ 90,318	$ 386,536	$ 86,272	$ 23,202	$ 80,246	$ 13,572	$ 586,381	$ 366,323	$ 311,961.48	$ 165,806
Savings in U$D	U$S 437	U$S 1870	U$S 417	U$S 112	U$S 388	U$S 66	2836	U$S 1772	U$S1,509	U$S 802
Savings (% per dose)	11.73%	26.67%	2.18%	7.50%	15.00%	8.72%	16.67%	27.08%	33.18%	10%
Savings per treatment local currency	$ 541,906	$ 1,546,144	$ 690,175	$ 92,807	$ 641,968	$ 67,860	$ 586,381	$ 3,663,232	$ 2,495,691.83	$ 1,658,056
Savings per treatment in U$D	U$S 2621.07	U$S 7478	U$S 3338	U$S 449	U$S3105	U$S 328	U$S19,853.39	U$S 17,718	U$S 12,071	U$S 8020

DISCUSSION

High-priced medicines constitute a challenge for health systems [2]. The exponential growth of the prices of these drugs has introduced a new concern among health financiers who find severe problems to maintain the benefits that they usually provide to their insurers due to the amount of money transferred to new treatments. Probably in the future the entire healthcare system will be threatened by the increasing costs of certain drugs, devices or technologies.

Limiting the provision of HPM based on their cost-effectiveness ratio has so far been unsuccessful since, despite negative reports from the scientific community, it increases lawsuit litigation and in many cases judges force insurers or governments to provide the treatments.

Strategies such as joint purchases among health providers (insurers and governments) have failed due to the existence of local or regional laws that prohibit the acquisition through these modalities.

For these reasons, dose-banding can be an alternative to at least partially solve this problem reducing costs and reassigning resources to other health needs. [6]

The savings observed in our study are significant and are a direct consequence from avoiding wastes of drugs. There are other potential benefits associated with dose banding like avoiding last-minute cancellations of prescriptions (they can be used later due drug stability – up to 28 days- or reassigned to another patient who needs the same dose).

For these purpose centralizing compounding (usually through outsourcing) is often necessary making possible to have enough number of doses to optimize commercial presentation of drugs and eventually redirect cancelled doses. [9]

Overstocking due to the provision of complete treatments versus only provision of actual doses is also an advantage for dose banding.

As observed in our study, using dose-banding generate savings of 15.87%. It should be noted that this saving does not include other variables that would also represent cost savings such as disposable material, personnel hours to prepare infusions and cost of bag of fluids for the medication among others. If these variables were included the savings might significantly increase.

CONCLUSION

Dose banding reduces costs and improve the access to cancer (and other life threating conditions) treatment. Reducing the waste of chemotherapy drugs it also has an environmental impact.

The result of this research shows how dose standardization results in significant savings (15,8%) and could be an option to reduce HPM expenditure in low-income countries as Argentina. If other variables are considered the savings would be increase.

These data encourage the development of new studies to assess the feasibility of the use of dose banding method in real cases to determine it feasibility in clinical settings.

Conflict of Interest

Declaration: Dr. Gustavo H. Marin & Dr. Dario Diaz Perez belongs to the national research system and declare no conflict of interest. Dr. Jose Maria Sanguinetti and Dr. Sebastian Alvarez are employees of Lis Pharma, a company that provides mixed medicines for general treatments. In order to avoid potential bias due to conflicts of interest, Dr. Sanguinetti and Dr. Alvarez were excluded from analysis phase and manuscript drafting (their role was limited to data provision).

Author Contribution

Jose Maria Sanguinetti and Dr. Sebastian Alvarez were in charge of data collection. Dr Gustavo H. Marin, Dr. Dario Diaz Perez performed the manuscript, analysis and last version of this paper. and its las version

REFERENCES

[1.] Paul H, Rajat K. El derecho humano a los medicamentos. Sur: Revista internacional de derechos humanos 2008; 5: 101-19

[2.] Marin GH, Cañas M, Marin G, Marin L, Nucher D, Diaz Pérez D, Urtasun M. Impacto económico de medicamentos de alto precio/costo en la Seguridad Social de Argentina. El caso del Instituto de Obra Social para las Fuerzas Armadas y de Seguridad [Economic impact of high-price/cost medicines on social security in Argentina. The case of the Institute for the Armed and Security Forces]. Medicina (B Aires). 2023;83(1):65-73..

[3.] Chatelut E, White-Koning ML, Mathijssen RH, Puisset F, Baker SD, Sparreboom A. Dose banding as an alternative to body surface area-based dosing of chemotherapeutic agents.Br J Cancer. 2012;107(7):1100-6

[4.] Retain MJ. Body-surface area as a basis for dosing of anticancer agents: science, myth, or habit?. J Clin Oncol 1998;16:7:2297-2298

[5.] Ogungbenro K, Patel A, Duncombe R, Nuttall R, Clark J, Lorigan P. Dose Rationalization of Pembrolizumab and Nivolumab Using PharHCMokinetic Modeling and Simulation and Cost Analysis. Clin PharHCMol Ther. 2018;103(4):582-590

[6.] Finch M, Masters N. Implications of parenteral chemotherapy dose standardisation in a tertiary oncology centre. J Oncol Pharm Pract. 2019 Oct;25(7):1687-1691. doi: 10.1177/1078155218812943. Epub 2018 Nov 6. PMID: 30400751.

[7.] Frödin JE. Why is intravenous chemotherapy cancelled and how often. Could it be prevented? A prospective analysis of all planned and given intravenous anti-tumor treatments at the Department of Oncology, Karolinska University Hospital, Stockholm during one month. Acta Oncol. 2015;54(7):1056-62. doi: 10.3109/0284186X.2014.990108. Epub 2015 Jan 16. PMID: 25591938.

[8.] NHS. Chemotherapy dose banding. National dose banding tables. UK. 2019. Disponible en: https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-b/b02/chemotherapy-dose-banding/

[9.] Sanguinetti JM, Martínez D, Abraham C, Chiapparoli J, Manfredi G, Streich F, Dimase F. Estandarización de dosis en tratamientos antineoplásicos, ¿puede ser el dose banding una alternativa eficiente para mejorar el acceso del paciente? Oncología Clínica 2022;; 27 (1): 49-52