ONCOLOGY PHARMACY PRACTICE

Commentary

J Oncol Pharm Practice
0(0) 1–4

DOI: 10.1177/1078155217706195
journals.sagepub.com/home/opp
SAGE

How can we ensure value for money from expenditure on injectable cancer drugs?

Peter J Gilbar[1,2] and Carole R Chambers[3]

Keywords
Cancer drugs, drug wastage, expenditure, stability, vial sizes

Date received: 27 March 2017; accepted: 29 March 2017

Global expenditure on cancer drugs is increasing at an alarming rate and consequentially is of considerable concern to consumers, health professionals and governments. Research progress has led to the continual introduction of novel high cost medications for use in the management of cancer, putting an enormous financial burden on society.[1,2] The ability to ensure equitable access to new innovative drugs and provide high-quality care to patients worldwide is virtually impossible in the current economic climate. The market for anticancer drugs is worth billions of dollars in the USA, ranking first by therapeutic class in terms of global spending.[3] Achieving global prices for cancer drugs that are equitable and consistent appears to be unachievable. While some nations regulate prices and reimbursement of high-cost cancer medications, this does not occur in every country, including the USA.[4] The pharmaceutical industry has been criticised for not doing enough to contain rising drug prices.[5,6] Strategies, involving minimal financial outlay to implement, have been proposed to ensure consumers receive better value for money spent on parenterally administered cancer medications. These include increasing the range of drug vial sizes available, ensuring vials contain some excess or overage, providing extended stability data, and ensuring drugs are supplied in the most suitable form for administration.[6–8]

A study we recently published in the journal *Future Oncology* identified numerous injectable cancer drugs that are amenable to strategies for reducing expenditure and avoiding drug wastage.[8] Information was obtained from 20 diverse countries on 45 drugs used in the treatment of malignancy. Data were sourced from the medication's Product Information (PI), if marketed, in each individual country. Pharmacists, the majority of whom were ISOPP members, provided data through a survey format. Drug availability was lowest in Kenya (37.8%) and highest in Australia and Germany (97.8%). Significant variations occurred in the availability of vial sizes between countries, with often only single vial sizes supplied for numerous medications. Information on overage was generally lacking. Stability data were inconsistent and variable between countries, with the majority of drugs only given a 24-h expiry.[8] A series of recommendations were developed. These were designed to achieve considerable monetary savings, not from a reduction in drug prices, but rather by minimising wastage of both drugs and time, and improving occupational safety.

Determination of the amount of money that could be saved was beyond the scope of the study as the acquisition cost of cancer medications varies widely, both between countries and within countries. Spending on cancer drugs, available in the USA as single dose vials, was investigated by Bach et al.[7] to evaluate the extent of drug wastage. By examining the

[1]Cancer and Palliative Care Services, Toowoomba Hospital, Toowoomba, Australia
[2]Rural Clinical School, Faculty of Medicine, The University of Queensland, Toowoomba, Australia
[3]Department of Cancer Services Pharmacy, Alberta Health Services, Alberta, Canada

Corresponding author:
Peter J Gilbar, Cancer and Palliative Care Services, Toowoomba Hospital, PMB 2, Toowoomba, QLD 4350, Australia.
Email: peter.gilbar@health.qld.gov.au

top 20 cancer drugs dosed by body size and packaged as single dose vials, they estimated the total amount of drug left over in vials after preparation for administration and calculated the resulting revenue received by drug companies for the unused and wasted drug. Discarded drug costs were judged to be in the billions. A perfect example of wastage that can occur is pembrolizumab, which was available as a 50 mg vial in 11 countries, in 2 countries as a 100 mg vial and only in the USA as both.[8] Pembrolizumab is dosed at 2 mg/kg; therefore, a 70 kg patient would require a dose of 140 mg. Utilising 50 mg vials (3×) the unused portion would be 10 mg. With 100 mg vials (2×), 60 mg would be left over. With this drug likely to have multiple indications in more and more countries in the near future and with treatment durations potentially lengthy, massive amounts of money can be involved. Despite being aware of the problem with vial sizes, the pharmaceutical industry has been slow to react. A 2007 Australian study examining the use of trastuzumab, available only as a 150 mg vial, in a medicine access program for metastatic breast cancer over a 40-month period, reported that 24% of trastuzumab was discarded.[9] Despite the authors concluding that an extra vial size could significantly reduce waste, it took another six years to introduce a 60 mg vial. Five countries surveyed still only have access to a 150 mg vial.[8]

Many anticancer drugs, once reconstituted and prepared for administration, are given very short expiry dates due to a lack of reliable stability data. Approved PI provides minimal extended stability data and what is provided is variable between countries.[8] Benziri et al.[10] reported a lack of stability data provided by manufacturers for compounded anticancer drugs. Data that were provided was mostly incomplete and difficult to put into practice, particularly for older drugs. Additional extrapolation and consensus on interpretation is frequently required to address issues not covered by data from manufacturers.[11] Stability studies performed by the pharmaceutical industry are only designed to fulfil licencing requirements and therefore are commonly restricted to 24 h for bacteriological reasons regardless of the true chemical stability, which in many cases could be longer.[12] A 2011 European consensus conference identified a need to close the gap in knowledge on drug stability for anticancer drugs between the insufficient data available in PI and what was required in clinical practice.[12] It was suggested that drug development programs of the pharmaceutical industry should generate enough stability data to allow for a more flexible clinical application and that these data be made available to the pharmacy community.

The ability to subcutaneously administer set dose drugs, such as denosumab, rituximab and trastuzumab, via a pre-filled syringe offers a number of advantages. Significant time and resources are saved as manufacturing is not required and administration is quicker, benefiting pharmacy, nursing, and patients. These formulations should have long-term stability and also reduce the risk of occupational exposure to staff handling them. Currently, these drugs are prepared for administration in a syringe from the vial using a range of methods from nursing staff on the bench to pharmacy staff in cytotoxic safety cabinets or isolators. These products do not contain preservatives so stability once drawn into a syringe is 24 h. Safe handling requirements during the preparation of MABs are still open to conjecture. While these agents do not pose the same occupational exposure risks as cytotoxic anticancer medications, there is still a need for safe handling guidelines to protect healthcare personnel. Recent reviews have concluded that safe handling data on MABs is based on low levels of information due to a lack of studies evaluating the risk of occupational exposure with these agents.[13–14] While uncertainties remain, a precautionary approach is warranted with consideration given to using interventions greater than for non-hazardous medications.[14]

A number of strategies were suggested to aid in the reduction of spending on cancer drugs.[8] The objective of these strategies is to achieve savings, not from reducing drug acquisition prices, but rather from better utilising current medications in order to achieve greater value for money by minimising wastage in both drugs and time, and improving occupational safety.

1. Guarantee the availability of a reasonable range of vial sizes in all countries in which drugs are marketed

If a range of drug vial sizes are already available in one country, it would seem reasonable that all countries, in which the drug is approved, have access to the same range. If only one vial size is available, government organisations should negotiate with industry to ensure that this is rectified before drug approval is given.

2. Encourage the use of vial sharing options

Vial sharing is a proven cost-saving method[15]: by making batches of doses of the same drug, quantities left in a vial, that would normally be discarded, can be used in the manufacture of the next product. Closed-system transfer devices can be used to extend the microbiological stability of anticancer drugs to facilitate vial sharing and subsequent cost savings.[16,17] In Australia, compounding company charges for commonly used

drugs are based on a per mg basis rather than on the standard per vial cost basis. Paying for only the quantity of drug that is actually used allows customers to make significant cost savings. Unfortunately, the practice of vial sharing is discouraged in a number of countries, including Japan and the USA. In the USA, both the Centers for Disease Control and Prevention and the US Pharmacopeial Convention call for single dose vials to be used only once.[18] Government organisations should review current legislation to permit vial sharing in manufacturing facilities with appropriate accreditation.

3. Explore the use of dose rounding and dose banding options

Dose rounding is the practice of rounding the prescribed dose of drug, either up or down, to that of the nearest whole vial strength available. This has been proposed to be successful when multiple vial sizes are available and rounding gives a difference of not greater than ±5% for cytotoxic agents and ±10% for MABs.[19–21] This approach has been criticised as it can lead to patients getting a too high or too low a dose but also that it does not actually reduce spending on leftover drug.[7] Dose banding is a system where doses that fall within defined ranges or bands are rounded up or down to predetermined standard doses with the maximum variation set at 5%.[22,23] This enables a range of pre-filled syringes or infusions to be manufactured or purchased which can then be used to administer the standard dose. NHS England is implementing a national system of dose banding and has introduced National Dose Banding Tables to ensure a standard approach of dose banding of chemotherapy across all Hospital Trusts.[24]

4. Guarantee that sufficient overage is available in vials for all parenteral drugs

A specific excess amount of drug, say 5%, should be provided in all vials to overcome problems of insufficient volume that can commonly arise during the reconstitution and manipulation of vials.[6]

5. Guarantee the availability of usable stability data on all manufactured products

The pharmaceutical industry invests billions of dollars in research and development in getting new anticancer drugs to the market place. Research should include stability studies to enable extended expiries for all prepared injectable drugs.[6] Study results should be published and made available for use by compounding companies and accredited manufacturing pharmacies.

6. Ensure that the most appropriate presentation forms are provided for all anticancer drugs

Drugs prescribed as set doses and fulfilling requirements of stability, storage, dosing volume and method of administration, should be provided as pre-filled syringes or pens.

Is there an incentive for the pharmaceutical industry to support the introduction of these recommended changes? The high price of drugs has been justified by pharmaceutical companies as necessary to support their investment in research and development.[25] Once a new drug is marketed, companies have a limited time to recoup outlay and maximise profits before patents expire and competing generic options become available. There is no motivation for them to introduce strategies to reduce drug wastage as this would result in less merchandise sold and a subsequent reduction in profits. The pharmaceutical companies are answerable to their shareholders and therefore not likely change their current approach to drug marketing without being forced to do so by the introduction of legislative changes.

The ability to streamline their formulation presentations on an international basis may be an incentive for the pharmaceutical industry. From our study, it appears that multiple presentations of the same product occur internationally, but with different vial sizes available in different countries. This was an interesting observation as one would have anticipated that global pharmaceutical companies would have introduced a "lean" approach to drug production. By standardising a suitable range of vials sizes that can be marketed in all countries, substantial cost savings can potentially be made. If the ability to gain market access for novel agents is impacted or competition arises within the same therapeutic space, this may provide motivation for industry to improve their current products by introducing better formulations and providing new stability information.

How can we, as oncology pharmacy practitioners, drive the implementation of these strategies on a global basis? If these strategies are to be successful it will require a drastic change in approach from many countries, probable changes in legislation, and the cooperation of the pharmaceutical industry, government organisations and healthcare professionals. Currently, in most countries, it is presumed that the pharmaceutical manufacturer determines which vials sizes and product presentations that they want to market. Government organisations, such as the FDA, do not have the statutory authority to dictate a certain vial size or delivery system. Unless legislative changes occur in all countries, collaboration becomes the most efficient option to effect change.

Oncology pharmacy is well represented by a number of professional organisations or societies at both an international, continental and national level. These include the International Society of Oncology Practitioners (ISOPP), European Society of Oncology Pharmacists, Hematology/Oncology Pharmacy Association, Canadian Association of Pharmacy in Oncology and British Oncology Pharmacy Association. As an organisation, ISOPP is in the process of forming alliances with a number of these groups with the aim of achieving common goals. The Global Oncology Pharmacy Summit, held prior to the ISOPP XVI in Budapest, can facilitate this process as a theme of the meeting is ''to mobilise the oncology pharmacy community around collaborative advocacy issues.'' We hope that these groups can assist in the promotion and dissemination of the results and recommendations of this research to governments at state, province and national levels.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Shih YT, Ganz PA, Aberle D, et al. Delivering high-quality and affordable care throughout the cancer care continuum. *J Clin Oncol* 2013; 31: 4151–4157.
2. Meropol NJ and Schulman KA. Cost of cancer care: issues and implications. *J Clin Oncol* 2007; 25: 180–186.
3. Howard DH, Bach PB, Berndt ER, et al. Pricing in the market for anticancer drugs. *J Econ Perspect* 2015; 29: 139–162.
4. Siddiqui M and Rajkumar SV. The high cost of cancer drugs and what we can do about it. *Mayo Clin Proc* 2012; 87: 935–943.
5. Angell M. Excess in the pharmaceutical industry. *CMAJ* 2004; 171: 1451–1453.
6. Gilbar PJ. Should the pharmaceutical industry be doing more to reduce the cost of cancer drugs? *J Pharm Prac Res* 2011; 41: 4–5.
7. Bach PB, Conti RM, Muller RJ, et al. Overspending driven by oversized single dose vials of cancer drugs. *BMJ* 2016; 352: i788.
8. Gilbar PJ, Chambers CR and Gilbar EC. Opportunities to significantly reduce expenditure associated with cancer drugs. *Future Oncol*. [in press] 2017.
9. Pearson SA, Ringland CL and Ward RL. Trastuzumab and metastatic breast cancer: trastuzumab use in Australia – monitoring the effect of an expensive medicine access program. *J Clin Oncol* 2007; 25: 3688–3693.
10. Benziri F, Bonan B, Ferrio AL, et al. Stability of antineoplastic agents in use for home-based intravenous chemotherapy. *Pharm World Sci* 2009; 31: 1–13.
11. De Lemos ML and Hamata L. Stability issues of parenteral chemotherapy drugs. *J Oncol Pharm Pract* 2007; 13: 27–31.
12. Bardin C, Astier A, Vulto A, et al. Guidelines for the practical stability studies of anticancer drugs: a European consensus conference. *Ann Pharm Fr* 2011; 69: 221–231.
13. Alexander M, King J, Bajel A, et al. Australian consensus guidelines for the safe handling of monoclonal antibodies for cancer treatment by healthcare personnel. *Intern Med J* 2014; 44: 1018–1026.
14. King J, Alexander M, Byrne J, et al. A review for the evidence for occupational exposure risks to novel anticancer agents – a focus on monoclonal antibodies. *J Oncol Pharm Pract* 2016; 22: 121–134.
15. Smith RSV. A 2-year retrospective review of vial sharing options for the compounding of cytotoxics. *Eur J Hosp Pharm* 2015; 22: 161–164.
16. Edwards MS, Solimando DA Jr, Grollman FR, et al. Cost savings realized by use of the PhaSeal® closed-system transfer device for preparation of antineoplastic agents. *J Oncol Pharm Pract* 2013; 19: 338–347.
17. Juhasz A, Batka G and Szucs A. Responding to drug shortages and rising costs: IV chemotherapy drug use optimization achieved by closed safety devices in hospital pharmacies. *Drugs Ther Perspect* 2016; 32: 170–176.
18. Lien K, Cheung MC and Chan KKW. Adjusting for drug wastage in economic valuations of new therapies for hematologic malignancies: a systematic review. *J Oncol Pract* 2016; 12: e369–379.
19. Dooley MJ, Singh S and Michael M. Implications of dose rounding of chemotherapy to the nearest vial size. *Support Care Cancer* 2004; 12: 653–656.
20. Field K, Zelenko A, Kosmider S, et al. Dose rounding of chemotherapy in colorectal cancer: an analysis of clinician attitudes and the potential impact on treatment costs. *Asia-Pac J Clin Oncol* 2010; 6: 203–209.
21. Francis SM, Heyliger A, Miyares MA, et al. Potential cost savings associated with dose rounding antineoplastic agents. *J Oncol Pharm Pract* 2015; 21: 280–284.
22. Plumridge RJ and Sewell GJ. Dose-banding of cytotoxic drugs: a new concept in cancer chemotherapy. *Am J Health-Syst Pharm* 2001; 58: 1760–1764.
23. Chatelut E, White-Konig ML, Mathijssen RHJ, et al. Dose banding as an alternative to body surface area-based dosing of chemotherapeutic agents. *Br J Cancer* 2012; 107: 1100–1106.
24. NHS England. How to use the NHS England dose banding tables, www.england.nhs.uk/commisioning/wp-content/uploads/sites/12/2013/05/dose-banding-tables-how-to.pdf (accessed 18 December 2016).
25. Kanttarjian HM, Fojo T, Mathisen M, et al. Cancer drugs in the United States: Justum Pretium – the just price. *J Clin Oncol* 2013; 31: 3600–3604.