Institution: University of Bath

Unit of Assessment: 3. Allied Health Professions, Dentistry, Nursing and Pharmacy

Title of case study: The establishment of 'dose-banding' for cytotoxic therapeutics - Bath Aseptic Services Unit, Ltd.

1. Summary of the impact

Doses of cytotoxic drugs for chemotherapy need to be determined on an individual basis for each patient and are generally calculated using Body Surface Area (BSA). Traditionally, this meant that doses of cytotoxic drugs needed to be prepared at 'the bedside', resulting in safety issues, significant wastage and placed an enormous burden on the time of healthcare workers. 'Dose-banding' is a system whereby chemotherapy doses, calculated using BSA or other means, are then fitted to pre-defined dose ranges, or 'bands'. This system allows for 'standard' syringes or infusions to be batch-prepared by the hospital pharmacy, or even pre-prepared and purchased from an external commercial source.

Research at the University of Bath, conducted between 2000 and 2007, pioneered the establishment of dose-banding as a practice and, through its spin-out commercialisation vehicle, Bath Aseptic Services Unit, Ltd. (Bath ASU), demonstrated that the batch production of cytotoxic drugs according to dose-banding is a viable commercial proposition.

Today, dose-banding is accepted around the world as a valid method of dosing cytotoxic therapies and, since 2008, has had a profound economic and social impact on the healthcare sector through improved patient care, changes to purchasing policy and improved health outcomes. In fact, the impact of dose-banding is so significant in the UK that NHS cancer trusts now recommend that *dose-banding should be implemented to manage capacity before investing in staff and facilities*.

Bath ASU now supplies over 150 NHS hospitals and pharmacies with upwards of 500,000 doses of injectable 'specials' per year (supplying around 30% of the entire UK commercial compounding market), employing over 70 full-time staff and currently generating revenues of over £20M per year.

2. Underpinning research

An initial research survey was conducted in 2000 by Professor Graham Sewell to investigate the concept and relative merits of dose-banding cytotoxic drugs, to identify which cytotoxic drugs were most amenable to dose-banding, and to address the primary issues relevant to implementing dose-banding into wider practice. The survey consisted of structured interviews with 17 pharmacists in 13 hospitals in England, Wales, and the Republic of Ireland that provided major cancer chemotherapy. Sewell subsequently organised a 'focus-group' meeting in August 2000 where the information resulting from the hospital survey was presented to the group, and a consensus on key issues was reached. This focus group was responsible for deriving the first formal definition for the practice of dose-banding. [1]

Sewell then conducted a study in 2004, funded by the University of Bath, to evaluate if variations existed between dose-banding and traditional individualised doses, using 5-fluorouracil (5-FU) as a prototypical chemotherapeutic. This study found that any differences observed were unlikely to be clinically significant, and that dose-banding of 5-FU should be clinically feasible [2].

Several pieces of research were also carried out to evaluate the viability of a commercial entity to produce and supply pre-prepared 'dose-banded' cytotoxics to hospitals. For this to be successful, two key criteria needed to be satisfied:

1. The drugs were stable (a) upon prolonged storage, and (b) to temperature variations, so as to enable delivery to the end user.

2. Valid banding schemes could be developed for each drug.

A sequential temperature cycling study was conducted in 2003 to investigate stability of the drug epirubicin when prepared as an infusion solution, and to facilitate its dose-banding. The physical

and chemical stability of epirubicin infusions were determined, with cycling between refrigerated storage and room temperatures to simulate in-use conditions. The study demonstrated the extended stability of epirubicin infusions and enabled batch-scale preparation of standard infusions for dose-banding schemes [3].

A subsequent study on carboplatin, published in 2007, developed a suitable banding scheme for the drug. The output from this research was significant as it represents the first published study identifying a dosing scheme that could be applied in practice, and was shown clinically to provide an effective treatment [4].

The research underpinning this impact case was conducted by Dr Graham Sewell (Professor of Clinical Pharmacy, employed 1998-2006), Dr Sarah Roberts (graduate student, enrolled 2002-2006) and Dr Sabine Kaestner (graduate student, enrolled 2003-2007), in the Department of Pharmacy & Pharmacology at the University of Bath.

3. References to the research

1. Plumridge, R.J. and Sewell, G.J. (2001) Dose-banding of cytotoxic drugs: a new concept in cancer chemotherapy, *American Journal of Health-System Pharmacy*, 58, 1760-1764. http://www.ajhp.org/content/58/18/1760.long
2. Kaestner S, Walker V, Roberts S, Perren T and Sewell G. (2004) Clinical and pharmacokinetic (PK) study on 'dose-banded' and individual-dose chemotherapy; an interim report. *Journal of Oncology Pharmacy Practice*, 10, 100. DOI: 10.1177/107815520401000201
3. Sewell, G., Rigby-Jones, A.E. and Priston, M.J. (2003) Stability of intravesical epirubicin infusion: a sequential temperature study, *Journal of Clinical Pharmacy and Therapeutics*, 28, 349-353. DOI: 10.1046/j.0269-4727.2003.00501.x
4. Kaestner, S. and Sewell, G. (2007) Dose-banding of carboplatin: rationale and proposed banding scheme, *Journal of Oncology Pharmacy Practice*, 13, 109-117. DOI: 10.1177/1078155207080801

4. Details of the impact

Impact Indicators:

Economic and commercial

Impact on Business

- Growth in revenue, growth in employee number, increased competitiveness:

Bath ASU was originally founded in June 2000. It supplied ready-to-use dose-banded cytotoxic drugs to NHS and private hospitals via third-party suppliers, and was one of the first fully commercial organizations to supply dose-banded therapeutics to the NHS. Following a management buy-out/buy-in in April 2006, Bath ASU switched to working as an independent, direct provider and moved to new, purpose-fitted premises in Corsham, Wiltshire. By 2008, Bath ASU employed 30 full time staff and produced approximately 200,000 products per year with annual revenues of approximately £5M.

The Managing Director of Bath ASU states [1]: *"Since 2008, Bath ASU has undergone significant growth. We now supply over 150 NHS hospitals and pharmacies with upwards of 500,000 doses of injectable 'specials' per year, employing over 70 full-time staff and now generating revenues of over £20M per year. Bath ASU will continue to expand in the coming years, with 2,500m^2 of new facilities in the building phase"*. Bath ASU now supplies ~30% of the entire UK commercial compounding market [1].

- Business creation and change of practice: New Business Sector

Bath ASU played a significant role in the establishing the acceptance of dose banded cytotoxic products within the medical profession. Their promotion of the concept has been through marketing initiatives, support for NHS training courses, Bath ASU's own external training packages and, of course,

promotion through its sales team. [1]

In addition to Bath ASU, there are now at least 12 other companies providing dose-banded cytotoxic products to the NHS [2]. These include a number of 'large pharma' companies, such as Eli Lilly, Hospira and Baxter, which have changed practice to now supply several of their own drugs in a pre-packaged, ready to use, dose-banded form.

- New products:

In 2008, only 7 drugs were available as pre-prepared dose-banded products [3]. This number has grown rapidly with 22 cytotoxic drug products being commercially available from Bath ASU by 2011 [2].

Impact on economy

- Reduced healthcare costs, reduced wastage, reduction in staff workload:

Early studies conducted by a number of NHS trust hospitals demonstrated that, if implemented, dose-banding could result in significant reductions in waste and in overtime of specialist staff [4]. For example, the introduction of dose-banding in a major Edinburgh cancer center was shown to decrease drug wastage to zero and to reduce specialist nurse overtime by 80% [5]. A study that considered 6 cytotoxic drugs reported that implementation of dose-banding had reduced direct costs by 4-14% [6]. In fact, the introduction of dose-banding into the NHS has had such profound impact that recent Guidelines published by the NHS North of England Cancer Network now recommend that the introduction of dose-banding should be undertaken to manage chemotherapy capacity before investing in staff and facilities [7]

Social

Impact on health

- Improved patient care, reduced treatment times, improved quality of life:

The implementation of dose banding within the NHS is considered to have many significant benefits, including [3,7]:

- Fewer dose calculation errors.
- Reduction in phone calls to prescribers or prescription alterations for dose-rounding.
- Quicker dispensing through use of pre-prepared doses (pre-filled syringes or infusions).
- Administration of chemotherapy on any chosen day is facilitated.
- Adoption of national contract pricing for chemotherapy (Scotland).
- Rationalisation of demand, with aseptic capacity liberated for more complex chemotherapy and more time for clinical duties.
- Reduced wastage by re-use of cancelled doses and avoidance of incomplete vial usage during production.
- Use of smaller syringe sizes making bolus administration easier.
- Easier processing of dose reductions at short notice.
- Supports treatment of patients closer to home.

Several of the above benefits were quantified in a pilot study conducted by the NHS at Derby Hospitals NHS Foundation Trust [8]. This project determined that implementation of dose-banding reduced patient waiting times by >60%. It also determined that the average time taken to prepare the drug regime was halved, as was the dispensing time for each dose.

Reach

The vast majority of dose-banded cytotoxic drugs are currently used within the UK [9]; however, in recent years, the benefits of dose-banding have begun to be recognized around the world. Bath ASU currently produces pre-prepared dose-banded cytotoxic drugs for use in the Republic of Ireland and in mainland Europe [1]. Furthermore, studies in a number of countries, such as Australia, have demonstrated the benefits of dose-banding within their own health-care systems [10].

5. Sources to corroborate the impact

All references cited here are publically available.

1. Letter from the Managing Director of Bath ASU Ltd.
2. Commercial Medicines Unit, Procurement guide: Dose-banding of cytotoxic pharmaceuticals. Department of Health, September (2011).
3. *Toolkit: How to Implement Dose banding of Chemotherapy*, by Andrew Gillian on behalf of Cancer Network Pharmacists Forum (2008). Available from: http://www.bopawebsite.org/contentimages/publications/Toolkit_Ver_3.0_FINAL.pdf
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