Chemotherapy Dose Banding

Development and Implementation

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Disclosure

Relevant Financial Relationship

- None

Off-label Investigational Uses

- None

Summary

- Learning Objectives
- Self Assessment Questions
- The Evolution of Dose Banding
- The Principles of Dose Banding
- Implementation by NHS England
- Evidence
- Relevance to Pharmacy Practice
- Review of the Self Assessment Questions
- Take-Home Messages

Learning Objectives

- Understand the principles of dose banding
- … and the benefits for patients, doctors and other providers
- Implementing in your own practice
- Next steps for standardising chemotherapy

Self-assessment questions

1. Can syringe size affect dose bands?

2. Do you think dose banding can be implemented in paediatrics?

3. If a drug has an absolute maximum dose (e.g. vincristine 2mg), should this be rounded to the nearest dose band?

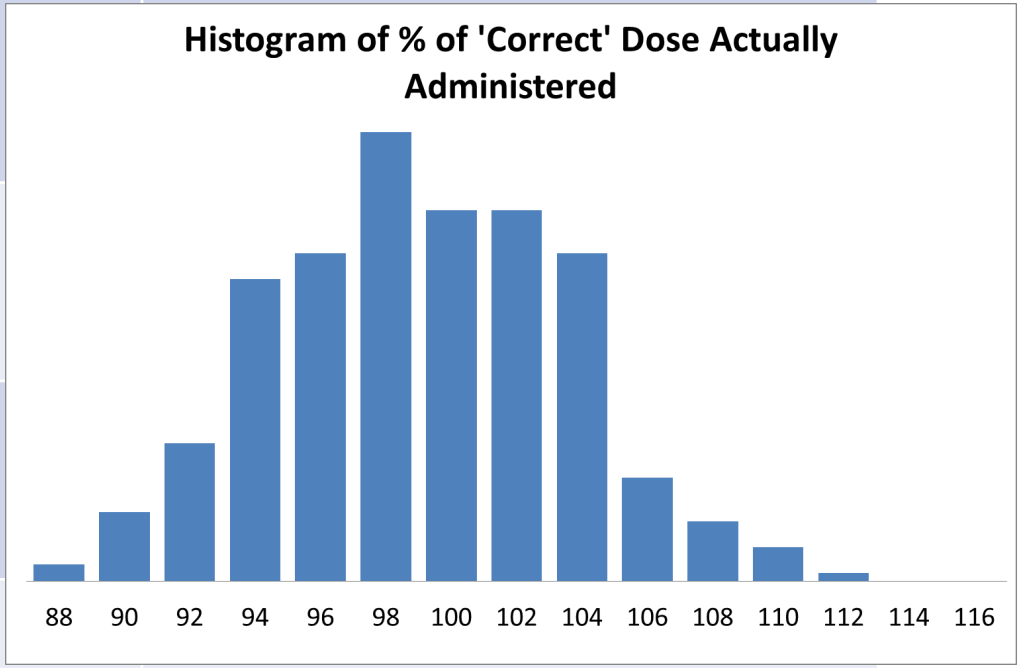
The Evolution of Dose Banding

How did we get there?

How accurate do our doses need to be?

How accurate do our doses need to be?

Pharmaceutical	Patient Size	Drug Handling
Labelled Vial Concentration ±5%	BSA Equation ±0.05m²	
Product Shelf-Life -5%	Height ±2.5cm	
In-use Shelf Life -10%	Weight ±1.5kg	
Syringe Accuracy ±4%		Distribution



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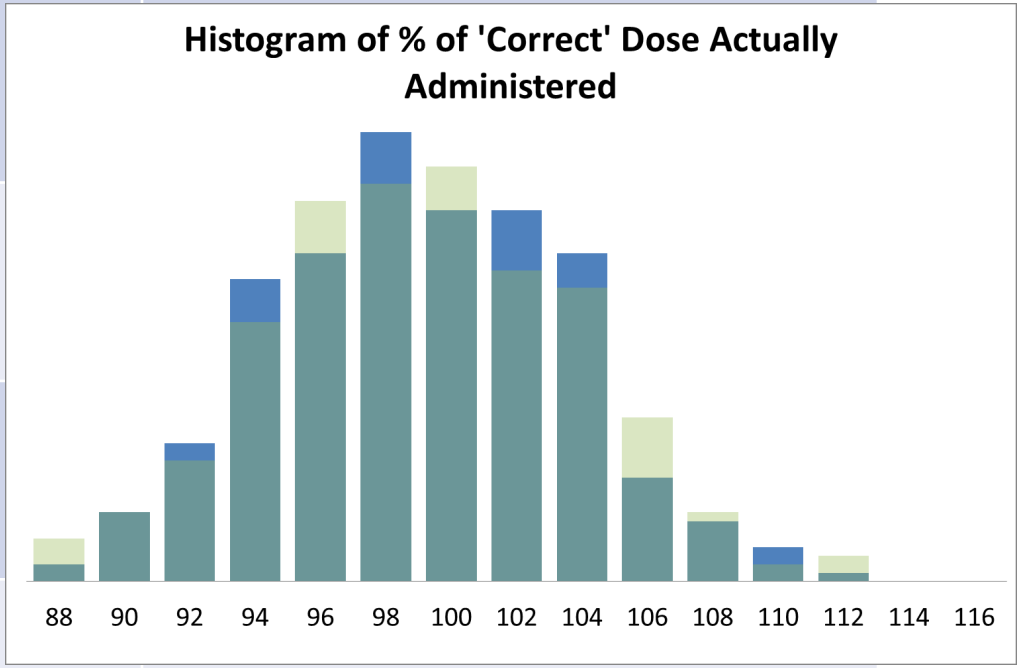


So why do it?

- ✓ Small number of syringe sizes needed to cover all doses – stock holdings do not need to be large
- ✓ Batch production has better QA and stability – long shelf life
- ✓ Buy in or prepare in advance (no on-the-day making) – no delays
- ✓ Remove from the fridge, label it, and send it up – fast dispensing
- ✓ Last minute cancellation? Return with a high chance of reuse – less wastage

Dose Banding Wars

Logarithmic

- ✓ Easy for 20% dose reductions
- ✓ Fewest possible doses
- ✗ Difficult for almost all other uses
- ✗ Doses not measurable

Surface Area Ranges

- ✗ Need new ranges for each mg/m^2 dose
- ✗ Decimal points vary in different systems (1.7mg vs 1.73m^2)
- ✗ Doesn't work for mg/kg or carbo

Dose Ranges

- ✓ Fewer doses if logarithmic-like
- ✓ Doses measurable
- ✓ Works for all dose methods incl. carbo
- ✓ Works for expensive drugs (vial rounding)

Principles of Dose Banding

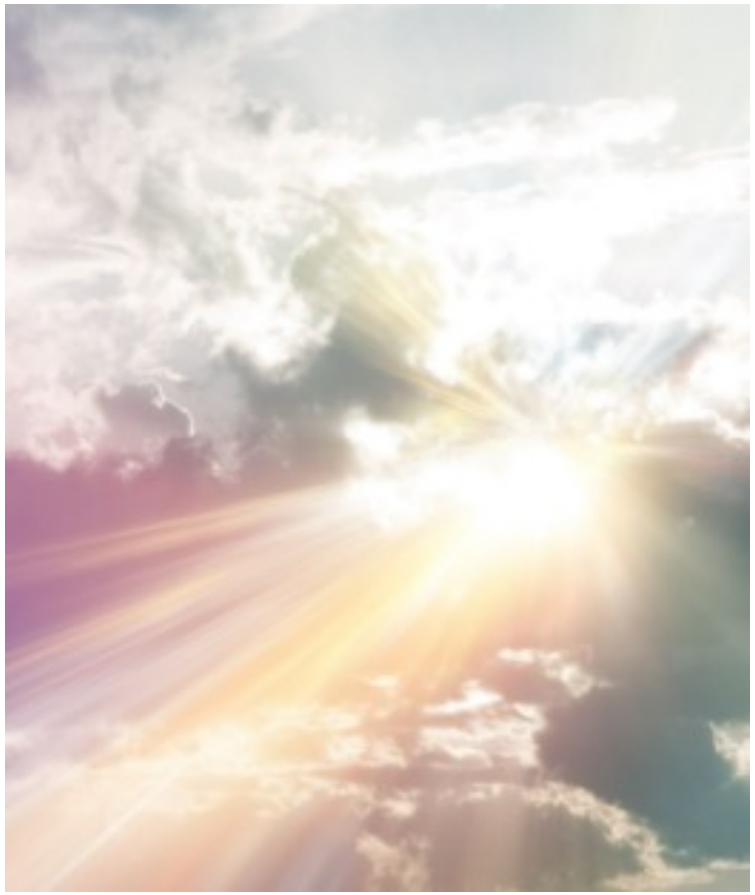
Of Systemic Anti-cancer Therapies

A new standard

- Working group in Manchester (Jan 2016) with pharmacists and pharmacokinetics researcher from:
  - 2 cancer hospitals (Marsden & Christie),
  - 1 district general hospital (Durham & Darlington),
  - 1 large teaching hospital (Sheffield)
- Three types of dose banding:
  - **Standard set of band volumes** (and doses) agreed for inexpensive drugs
  - **High cost drugs** (rounded to nearest vial sizes or fractions)
  - **Multiple syringe method** ('pick and mix') for syringe pumps
- Note it is the volume-derived doses that are banded (not surface area or patient weight etc.)
- Therefore the dose calculation method (mg/m^2 etc.) *does not matter*

The Volume Epiphany

- When banding many drugs the SAME VOLUMES kept appearing – because they're easy to draw up
- Why not have one set of volumes instead? ONE SET!
- Doses would derive from that volume set *for any drug based on its concentration*



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Measurable	85% Fill Whole Graduations	**Containers**	n + 1	**Max Dose**	Will be a band

Implementation by NHS England

Standardising across an entire health economy

Stakeholder forums and training days

- **NHS Clinical Reference Groups (CRGs)** – clinicians, experts, commissioners, patients who *advise the NHS on service provision*
  - **Medicines Optimisation CRG** – Dose standardisation group created here!
  - **Cancer CRG**
- **NHS Pharmaceutical Aseptic Services Group (PASG)** – *advise NHS on aseptic prep.*
- **Pharmacists:** BOPA (oncology pharmacists)
- **Nurses:** UKON (oncology nurses)
- **Clinicians:** Royal College of Physicians
- **Commercial Suppliers:** Work **18 months in advance**

Maintenance (New Drugs)

NHS England Dose Standardisation Group

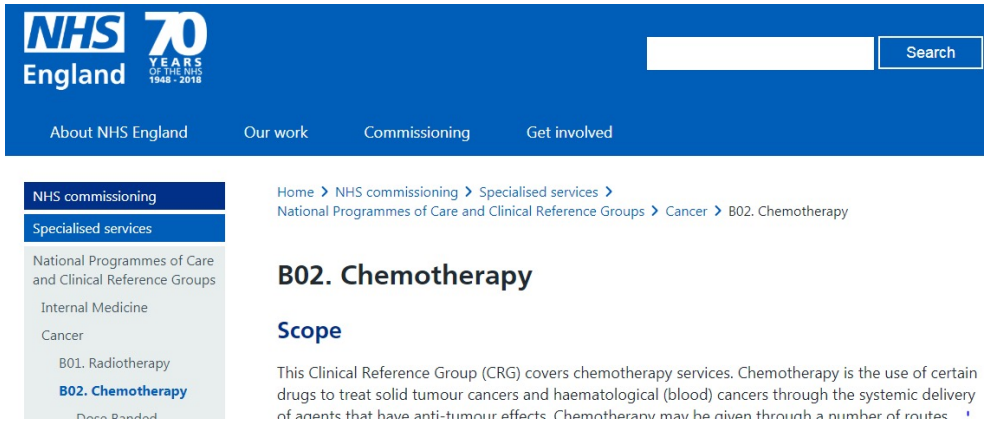
- Meet monthly to work on new drug tables
- Tables used in the NICE application process

National Institute for Clinical Excellence (NICE)

- Assess new drugs for use for in the NHS
- Banding tables assist in the financial assessment of cost and wastage

Published Tables NHS England website

- https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-b/b02/



Standardise product presentation

- **Fluid type** If drug stable in >1 fluid type (glucose, NaCl) agree one
- **Volume** Variable volume drugs have bag sizes which have overlapping dose ranges
  Agree upper & lower doses for each bag

Paclitaxel	Dose range for each bag size					
Bag choice		overlap		overlap		
100mL	30	to	120			
250mL		75	to		300	
500mL				150	to	600

- **Storage** (protect from light, refrigerate)
- **Expiry** Agree format: best before vs use by vs do not use after

If we all use the SAME product we can purchase together

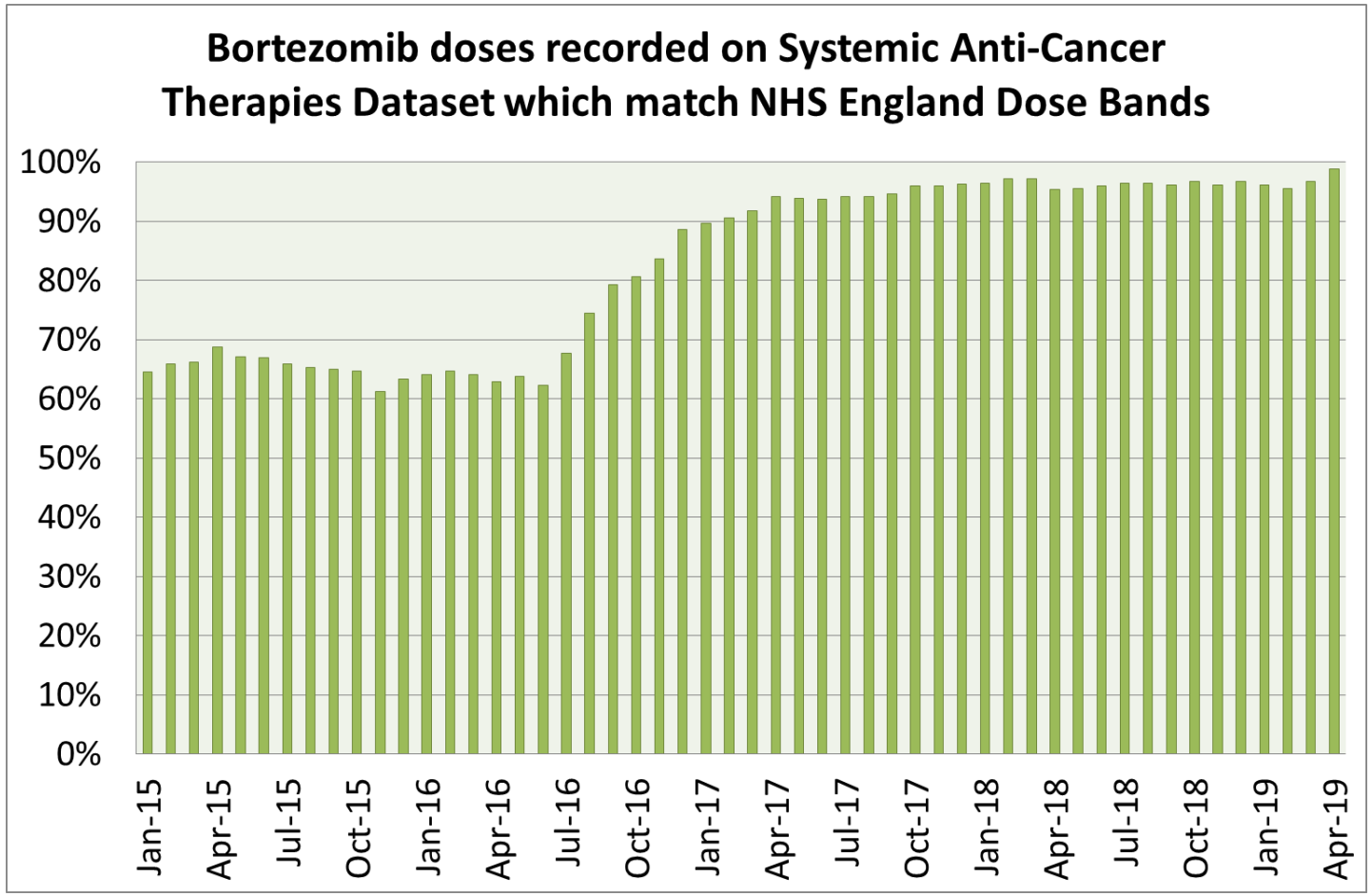
Other problems & solutions

- **Gemcitabine** now has licenced bands
  vol varied between doses – not usual practice
- **Gemcitabine** 2 concs - 38mg/mL & 100mg/mL
  Separate tables – *pick one!*

  What if supplier uses 100mg/mL for batched doses and you make the others with 38mg/mL?
  Avoid – use same strength / amend rare doses

- **5-FU** 2 concs - 25mg/mL & 50mg/mL
  1 double the other. Use 50mg/mL for banding double the volume to get 25mg/mL doses
- *Doubling a volume will usually give a measurable dose – but halving a volume may not*

Implementation - Progress



Bortezomib

Data from 259,851 doses

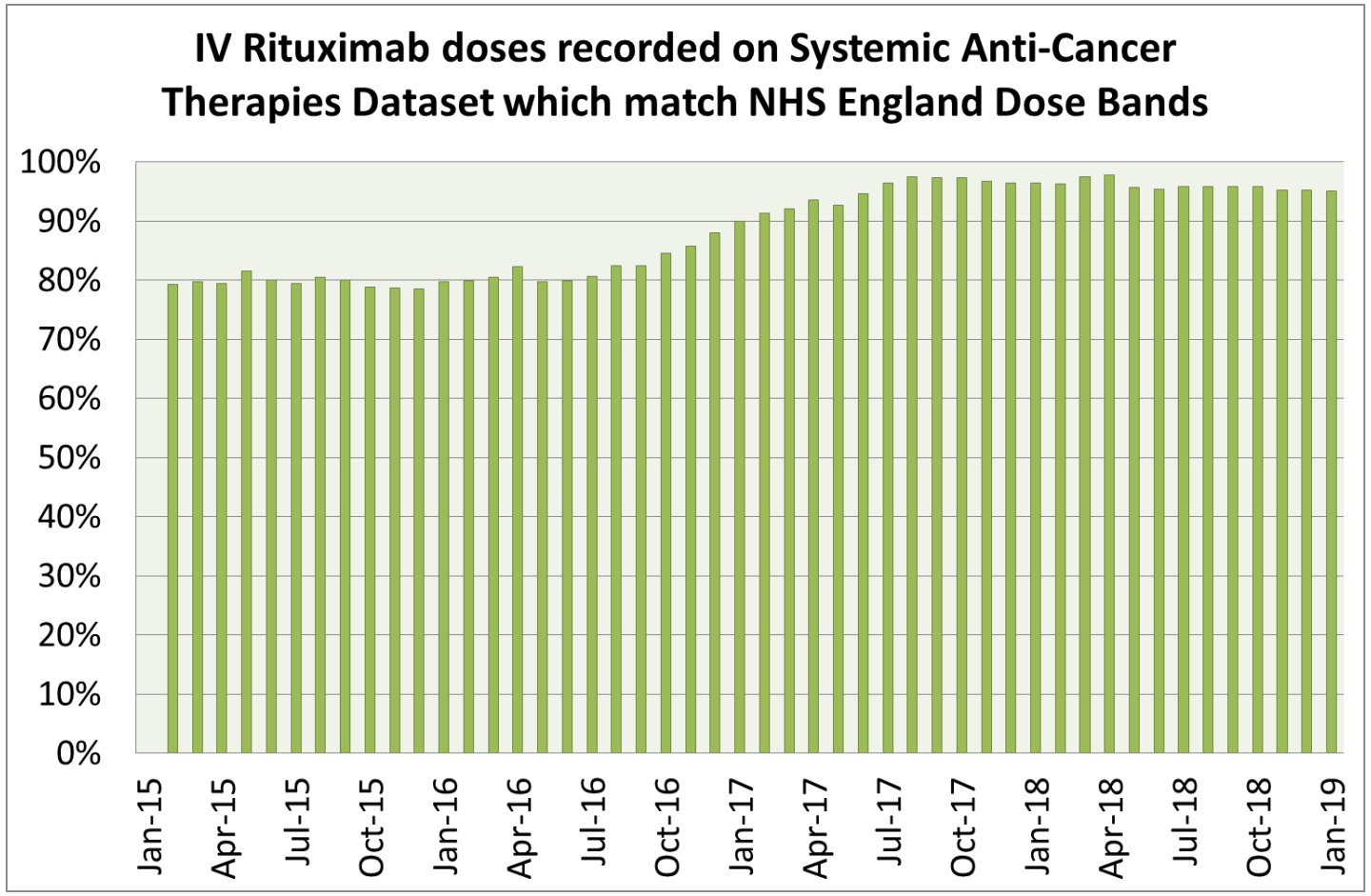
Jan-Mar 2015:

- 67 different doses
- Top 5 doses = 58% of administrations

Jan-Mar 2019:

- >90% of administrations in 5 bands (1.8, 2, 2.25, 2.5, 2.75mg)

Implementation - Progress



Rituximab (Haematology)

Data from 174,401 doses

Jan-Mar 2015:

- 62 different doses
- Top 5 doses = 74% of administrations

Oct-Dec 2018:

- >85% of administrations in 5 bands (600, 650, 700, 800, 900mg)

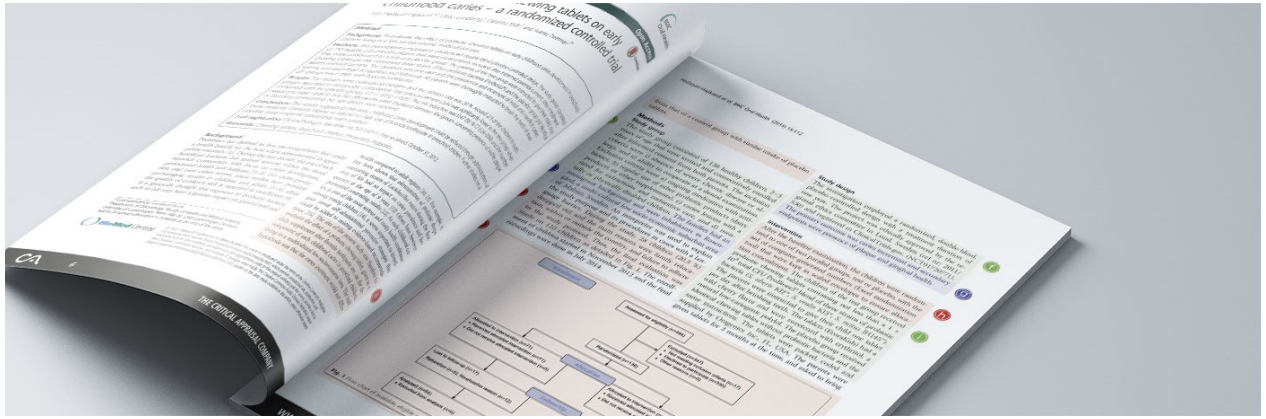
Evidence

Is more required?

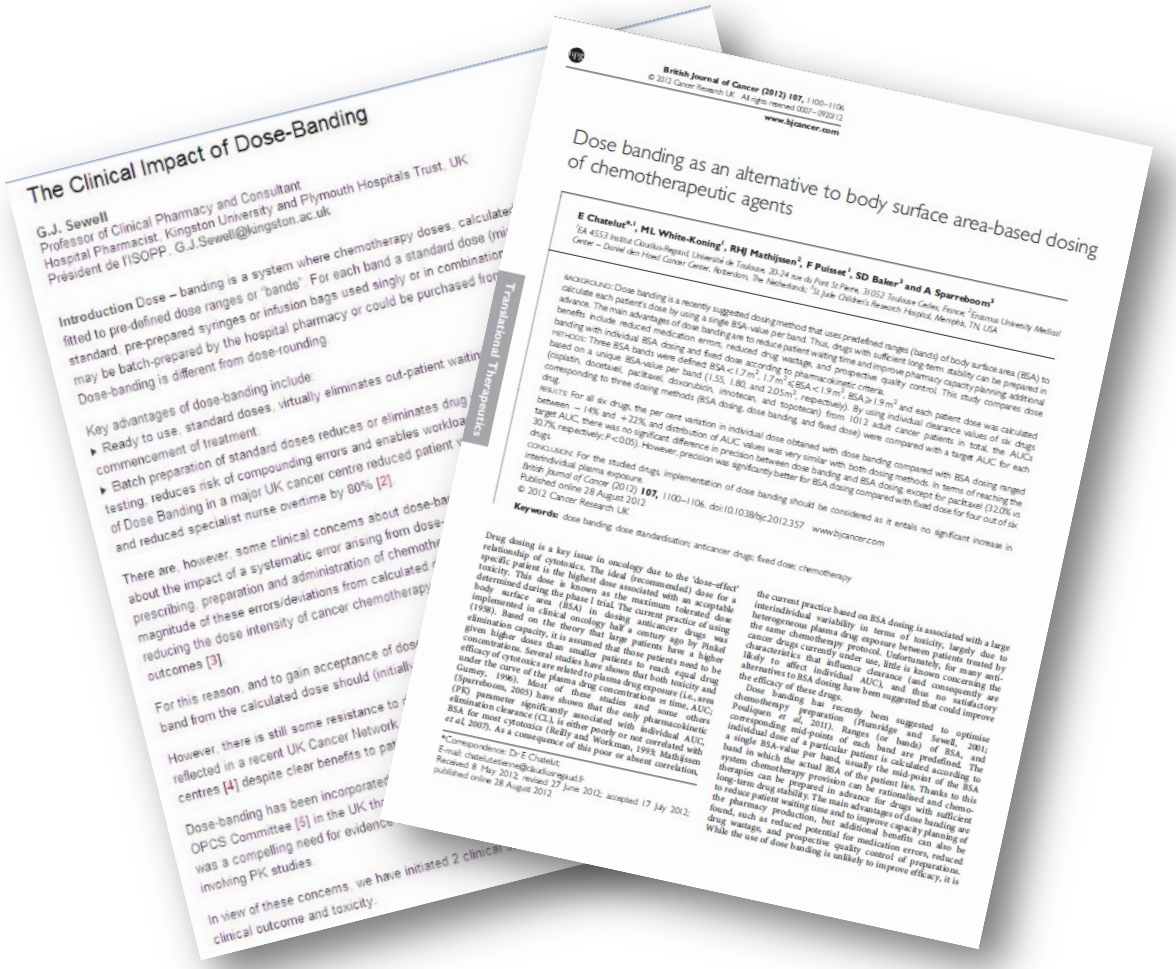
Evidence

- Is dose banding having any clinical effect on cancer treatment?
- More and more papers are being published in support of dose banding including:
  - Standard chemotherapy
  - Monoclonal antibodies
  - Paediatrics (children appear to have no ill effects, but infants require more data)

But we'd like more…



Standard Chemotherapy



The Clinical Impact of Dose-Banding

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Introduction Dose – banding is a system where chemotherapy doses, calculated fitted to pre-defined dose ranges or "bands". For each band a standard dose (mi standard, pre-prepared syringes or infusion bags used singly or in combination may be batch-prepared by the hospital pharmacy or could be purchased fro Dose-banding is different from dose-rounding.

Key advantages of dose-banding include:
- Ready to use, standard doses, virtually eliminates out-patient waitin commencement of treatment.
- Batch preparation of standard doses reduces or eliminates drug testing, reduces risk of compounding errors and enables workloa of Dose Banding in a major UK cancer centre reduced patient and reduced specialist nurse overtime by 80% [2].

There are, however, some clinical concerns about dose-ba about the impact of a systematic error arising from dose- prescribing, preparation and administration of chemoth magnitude of these errors/deviations from calculated reducing the dose intensity of cancer chemotherapy outcomes [3].

For this reason, and to gain acceptance of dos band from the calculated dose should (initiall

However, there is still some resistance to reflected in a recent UK Cancer Network centres [4] despite clear benefits to pa

Dose-banding has been incorporated OPCS Committee [5] in the UK th was a compelling need for evidence involving PK studies.

In view of these concerns, we have initiated 2 clinic clinical outcome and toxicity.

Translational Therapeutics

British Journal of Cancer (2012) 107, 1100–1106
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www.bjcancer.com

Dose banding as an alternative to body surface area-based dosing of chemotherapeutic agents

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BACKGROUND: Dose banding is a recently suggested dosing method that uses predefined ranges (bands) of body surface area (BSA) to calculate each patient's dose by using a single BSA-value per band. Thus, drugs with sufficient long-term stability can be prepared in advance. The main advantages of dose banding are to reduce patient waiting time and improve pharmacy capacity planning, additional benefits include reduced medication errors, reduced drug wastage, and prospective quality control. This study compares dose banding with individual BSA dosing and fixed dose according to pharmacokinetic criteria.

METHODS: Three BSA bands were defined: BSA < 1.7 m², 1.7 m² ≤ BSA < 1.9 m², BSA ≥ 1.9 m² and each patient dose was calculated based on a unique BSA-value per band (1.55, 1.80, and 2.05 m², respectively). By using individual clearance values of six drugs (cisplatin, docetaxel, paclitaxel, doxorubicin, irinotecan, and topotecan) from 1012 adult cancer patients in total, the AUCs corresponding to three dosing methods (BSA dosing, dose banding, and fixed dose) were compared with a target AUC for each drug.

RESULTS: For all six drugs, the per cent variation in individual dose obtained with dose banding compared with BSA dosing ranged between −14% and +22%, and distribution of AUC values was very similar with both dosing methods. In terms of reaching the target AUC, there was no significant difference in precision between dose banding and BSA dosing except for paclitaxel (32.0% vs 30.7%, respectively; $P<0.05$). However, precision was significantly better for BSA dosing compared with fixed dose for four out of six drugs.

CONCLUSION: For the studied drugs, implementation of dose banding should be considered as it entails no significant increase in interindividual plasma exposure.

British Journal of Cancer (2012) 107, 1100–1106. doi:10.1038/bjc.2012.357 www.bjcancer.com
Published online 28 August 2012
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Keywords: dose banding; dose standardisation; anticancer drug; fixed dose; chemotherapy

Drug dosing is a key issue in oncology due to the 'dose-effect' relationship of cytotoxics. The ideal (recommended) dose for a specific patient is the highest dose associated with an acceptable toxicity. This dose is known as the maximum tolerated dose determined during the phase I trial. The current practice of using body surface area (BSA) in dosing anticancer drugs was implemented in clinical oncology half a century ago by Pinkel (1958). Based on the theory that large patients have a higher elimination capacity, it is assumed that those patients need to be given higher doses than smaller patients to reach equal drug concentrations. Several studies have shown that both toxicity and efficacy of cytotoxics are related to plasma drug exposure (i.e., area under the curve of the plasma drug concentrations as time, AUC; Gurney, 1996). Most of these studies and some others (Sparreboom, 2005) have shown that the only pharmacokinetic (PK) parameter significantly associated with individual BSA for most cytotoxics (CL), is either poorly or not correlated with elimination clearance (Relling and Workman, 1993; Mathijssen et al, 2007). As a consequence of this poor or absent correlation, the current practice based on BSA dosing is associated with a large interindividual variability in terms of toxicity, largely due to heterogeneous plasma drug exposure between patients treated by the same chemotherapy protocol. Unfortunately, for many anti-cancer drugs currently under use, little is known concerning the characteristics that influence clearance (and consequently are likely to affect individual AUC), and thus no satisfactory alternatives to BSA dosing have been suggested that could improve the efficacy of these drugs.

Dose banding has recently been suggested to optimise chemotherapy preparation (Plunkett and Sewell, 2001; Poolgreen et al, 2011). Ranges (or bands) of BSA, and corresponding mid-points of each band are predefined. The individual dose of a particular patient is calculated according to a single BSA-value per band, usually the mid-point of the BSA band in which the actual BSA of the patient lies. Thanks to this system chemotherapy provision can be rationalised and chemotherapies can be prepared in advance for drugs with sufficient long-term drug stability. The main advantages of dose banding are thus pharmacy waiting time and to improve capacity planning of pharmacy production, but additional benefits can also be found, such as reduced potential for medication errors, reduced drug wastage, and prospective quality control of preparations. While the use of dose banding is unlikely to improve efficacy, it is

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Received 8 May 2012; revised 27 June 2012; accepted 17 July 2012; published online 28 August 2012

GJ Sewell, 2006

- Dose banding 5-FU made no difference to the AUC exposure to patients

E Chatelut, 2012

- 6 drugs tested: Cisplatin, docetaxel, paclitaxel, doxorubicin, irinotecan, topotecan – no significant difference in AUC / plasma exposure

In general – inter-patient variation in drug handling was more than anything contributed by dose banding in AUC exposure

Monoclonal antibodies & biologics

New Drug Development and Clinical Pharmacology

The Oncologist®

Fixed Dosing of Monoclonal Antibodies in Oncology

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Monoclonal antibodies • Cancer • Fixed dosing

ABSTRACT

Most monoclonal antibodies in oncology are administered in body–size-based dosing schedules. This is believed to correct for variability in both drug distribution and elimination between patients. However, monoclonal antibodies typically distribute to the blood plasma and extracellular fluids only, which increase less than proportionally with the increase in body weight. Elimination takes place via proteolytic catabolism, a nonspecific immunoglobulin G elimination pathway, and intracellular degradation after binding to the target. The latter is the primary route of elimination and is related to target expression levels rather than body size. Taken together, the minor effects of body size on distribution and elimination of monoclonal antibodies and their usually wide therapeutic window do not support body–size-based dosing. We evaluated effects of body weight on volume of distribution and clearance of monoclonal antibodies in oncology and show that a fixed dose for most of these drugs is justified based on pharmacokinetics. A survey of the savings after fixed dosing of monoclonal antibodies at our hospital showed that fixed dosing can reduce costs of health care, especially when pooling of preparations is not possible (which is often the case in smaller hospitals). In conclusion, based on pharmacokinetic parameters of monoclonal antibodies, there is a rationale for fixed dosing of these drugs in oncology. Therefore, we believe that fixed dosing is justified and can improve efficiency of the compounding. Moreover, drug spillage can be reduced and medication errors may become less likely. *The Oncologist* 2017;22:1–10

Implications for Practice: The currently available knowledge of elimination of monoclonal antibodies combined with the publicly available data from clinical trials and extensive population pharmacokinetic (PopPK) modeling justifies fixed dosing. Interpatient variation in exposure is comparable after body weight and fixed dosing and most monoclonal antibodies show relatively flat dose-response relationships. For monoclonal antibodies, this results in wide therapeutic windows and no reduced clinical efficacy after fixed dosing. Therefore, we believe that fixed dosing at a well-selected dose can increase medication safety and help in reduction of costs of health care without the loss of efficacy or safety margins.

INTRODUCTION

Today, in the field of oncology, most drugs are administered in a body–size-based dosing schedule instead of a fixed dose for all patients. For most cytotoxic small molecule anticancer agents, body surface area (BSA) (in m^2) is used for dosing. The origin of BSA-based dosing is related to the narrow therapeutic window of these antineoplastic agents [1]. By comparing the maximum tolerated dose (MTD) in humans to the MTD in different animal species used in preclinical experiments, it was observed that MTDs were comparable when expressed in milligram per m^2 [2], [3]. This allowed a safer setting of the starting dose and dose escalation of new agents in phase I studies [1]. The acceptance of dosing in mg/m^2 was further fueled by the general belief that pharmacokinetic parameters like clearance can be scaled between individuals according to BSA [1, 4]. Dosing in milligram per m^2 is, therefore, considered to correct for variability in drug distribution and elimination observed after fixed dosing. However, BSA-based dosing is still under debate since there is a lack of clinical trial data that BSA-based dosing indeed reduces interindividual variation in drug exposure [5]. A large meta-analysis by McLeay et al. [6] showed that BSA, lean

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JJMA Hendrikx, 2017

- First significant paper on mabs
- Wide therapeutic window / flat dose-response relationship
- No reduced clinical efficacy after fixed dosing
- Most mabs can be ‘rounded’ to 1 or 2 ‘bands’

- We use 10% variance for mabs – conservative
- More than half of new mabs have flat doses
- Remember 10% *does not* apply to conjugates!

Monoclonal antibod

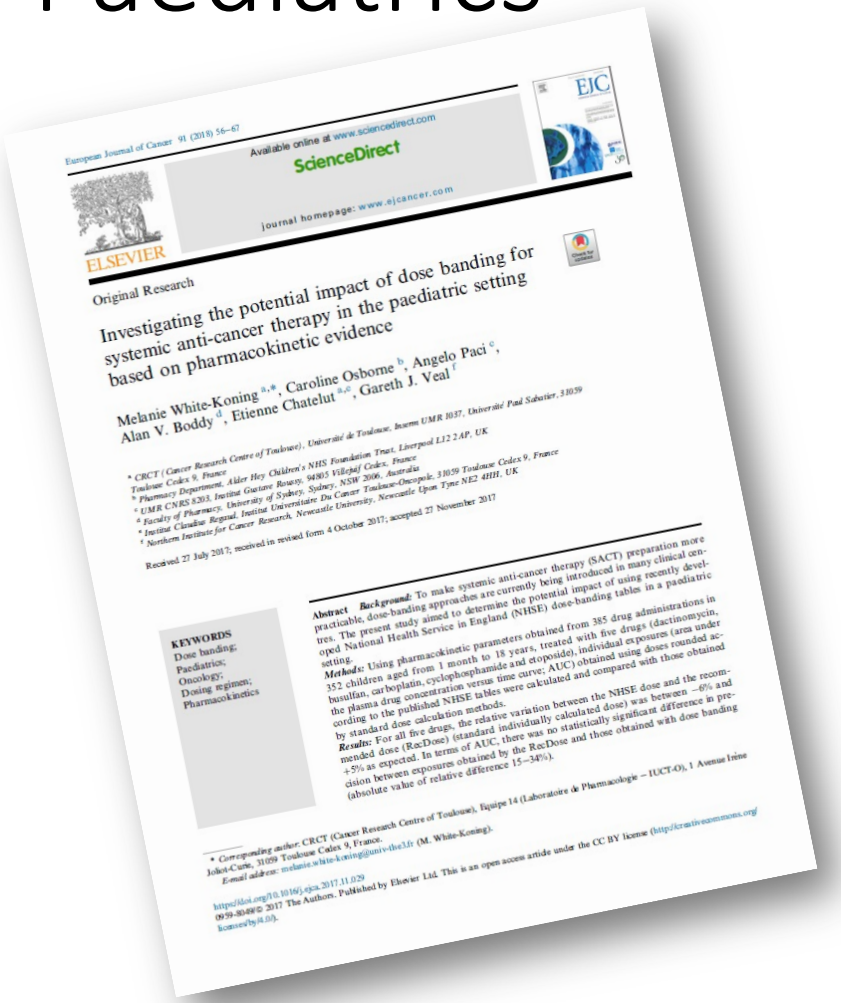
Table 1. Monoclonal antibodies approved for treatment of cancer and a proposal for fixed dosing

Generic name	Approved dose	Therapeutic window[a]	Volume of distribution at steady state (L)	Body weight effect on volume of distribution[b]	Clearance (L/day)	Body weigh effect on clearance[b]
Bevacizumab	5 mg/kg; 2 weekly 10 mg/kg; 2 weekly 15 mg/kg; 3 weekly	5–15 mg/kg	2.66	0.411	0.207	0.368
Catumaxomab	Day 0: 10 ug Day 3: 20 ug Day 7: 50 ug Day 10: 150 ug	*Intraperitoneal administration with limited absorption into the systemic circulation.*				
Cetuximab	250 mg/m^2 weekly (400 mg/m^2 loading dose)	250–400 mg/m^2	5.22	0.42 (effect of BSA was evaluated)	0.497	None
Ipilimumab	3 mg/kg; 3 weekly	3–10 mg/kg	4.15	0.708	0.360	0.642
Nivolumab	3 mg/kg; 2 weekly	1–10 mg/kg	8.0	0.580	0.228	0.707
Obinutuzumab	1,000 mg per cycle (cycle 2–6)	1,000–2,000 mg	2.76	0.383	0.083	0.231
Ofatumumab	1,000 mg; 4 weekly (untreated CLL) 2,000 mg; weekly (refractory CLL)	1,000–2,000 mg	3.26	0.076	0.369	0.229
Panitumumab	6 mg/kg; 2 weekly	2.5–9 mg/kg	3.66	0.526	0.269	0.411
Pembrolizumab	2 mg/kg; 3 weekly	1–10 mg/kg	8.1	0.489	0.23	0.595
Pertuzumab	420 mg; 3 weekly (840 mg loading dose)	420–1,050 mg	3.07	0.747	0.239	0.516–0.589
Ramucirumab	8 mg/kg; 2 weekly	8–10 mg/kg	5.5	Not reported	0.336	Not reporte
Rituximab	375 mg/m^2; interval is variable	375–2,250 mg	2.98	0.73	0.257	1.02
Trastuzumab	2 mg/kg/week (with an additional 2 mg/kg as loading dose)	1–>8 mg/kg	2.95	0.556	0.225	1.07

Fixed dose is proposed if the effect of body weight on the volume of distribution and clearance is minimal (<0.5). If the effect reported, a fixed dosing approach might be considered for practical reasons.
[a]The therapeutic window is based on a minimum effective dose at the interval of the approved dose and a maximum tolerated (or
[b]The effect is presented as the exponent used in population pharmacokinetics models in formula 1 to correct for the effect of bod
Abbreviations: BSA, body surface area; EMA, European Medicines Agency; CLL, chronic lymphocytic leukemia.

Generic name	Proposed fixed dose
Bevacizumab	40–140 kg: 600 mg, 2 weekly
Catumaxomab	*Approved fixed dose*
Cetuximab	1.3–2.2 m^2: 500 mg, weekly (with 800 mg loading dose)
Ipilimumab	40–60 kg: 150 mg, 3 weekly 60–100 kg: 250 mg, 3 weekly 100–140 kg: 350 mg, 3 weekly
Nivolumab	40–140 kg: 240 mg, 2 weekly
Obinutuzumab	*Approved fixed dose*
Ofatumumab	*Approved fixed dose*
Panitumumab	40–80 kg: 300 mg, 2 weekly 80–140 kg: 500 mg, 2 weekly
Pembrolizumab	40–140 kg: 150 mg, 3 weekly
Pertuzumab	*Approved fixed dose*
Ramucirumab	*Insufficient data*
Rituximab	1.3–2.2 m^2: 800 mg per administration
Trastuzumab	40–140 kg: 450 mg, 3 weekly

Paediatrics



European Journal of Cancer 91 (2018) 56–67

Available online at www.sciencedirect.com

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Original Research

Investigating the potential impact of dose banding for systemic anti-cancer therapy in the paediatric setting based on pharmacokinetic evidence

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Received 27 July 2017; received in revised form 4 October 2017; accepted 27 November 2017

KEYWORDS
Dose banding;
Paediatrics;
Oncology;
Dosing regimen;
Pharmacokinetics

Abstract **Background:** To make systemic anti-cancer therapy (SACT) preparation more practicable, dose-banding approaches are currently being introduced in many clinical centres. The present study aimed to determine the potential impact of using recently developed National Health Service in England (NHSE) dose-banding tables in a paediatric setting.
Methods: Using pharmacokinetic parameters obtained from 385 drug administrations in 352 children aged from 1 month to 18 years, treated with five drugs (dactinomycin, busulfan, carboplatin, cyclophosphamide and etoposide), individual exposures (area under the plasma drug concentration versus time curve; AUC) obtained using doses rounded according to the published NHSE tables were calculated and compared with those obtained by standard dose calculation methods.
Results: For all five drugs, the relative variation between the NHSE dose and the recommended dose (RecDose) (standard individually calculated dose) was between −6% and +5% as expected. In terms of AUC, there was no statistically significant difference in precision between exposures obtained by the RecDose and those obtained with dose banding (absolute value of relative difference 15–34%).

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https://doi.org/10.1016/j.ejca.2017.11.029
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- Tested 5 drugs: dactinomycin, busulfan, carboplatin, cyclophosphamide and etoposide
- Compared AUC of calculated doses with NHS England dose bands
- No statistical difference seen

Some benefits of banding not seen in paediatrics:

- Wider spread of doses, lower use of each dose – higher risk of wastage
- Smaller bag volumes (non-standard) – unlikely to be batched with adults

Relevance to Pharmacy Practice

- Pharmacy is the driving force behind dose banding
- Pharmacists devised the dose banding method and tables
  - are behind the published papers of evidence
  - have educated the wider clinical teams,
  - have surveyed, and sought clinical approval
  - are designing the standard product definitions
  - are liaising with industry for cheaper batches & supply
  - adjust chemotherapy doses on prescriptions to dose bands

Future Perspectives

- The future is already here in the UK
- Licenced products are becoming available – 1 already in use
- Expecting 2 or 3 this year
- Manufacturing industry now liaise with us in advance
- Batch purchasing of pre-made bands accounts for a considerable percentage of our inventory – we're working towards 70%
- Group purchasing with other hospitals is the next step
- Our dose tables are available online!

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Take-Home Messages

- It is possible to use two systems to dose band, and between them band chemotherapy, biological agents and paediatrics
- Don’t stop with just the dose - standardise your product definitions (volumes and fluids) too
- Buy in batches and reduce costs