Tercera Reunión Anual del grupo:

GEDEFO

Grupo de Farmacia Oncológica de la SEFH

sefh
Sociedad Española
de Farmacia Hospitalaria

fefh
Fundación Española
de Farmacia Hospitalaria

ATENCIÓN FARMACÉUTICA
AL PACIENTE ONCOHEMATOLÓGICO

Dose Banding
Estrategias de implantación
Experiencia europea

Richard Nuttall
The Royal Marsden, Londres

Overview

- History of dose banding in the UK and the principles it produced
- How we implemented dose banding
- Problems and resolutions
- Evidence in clinical practice

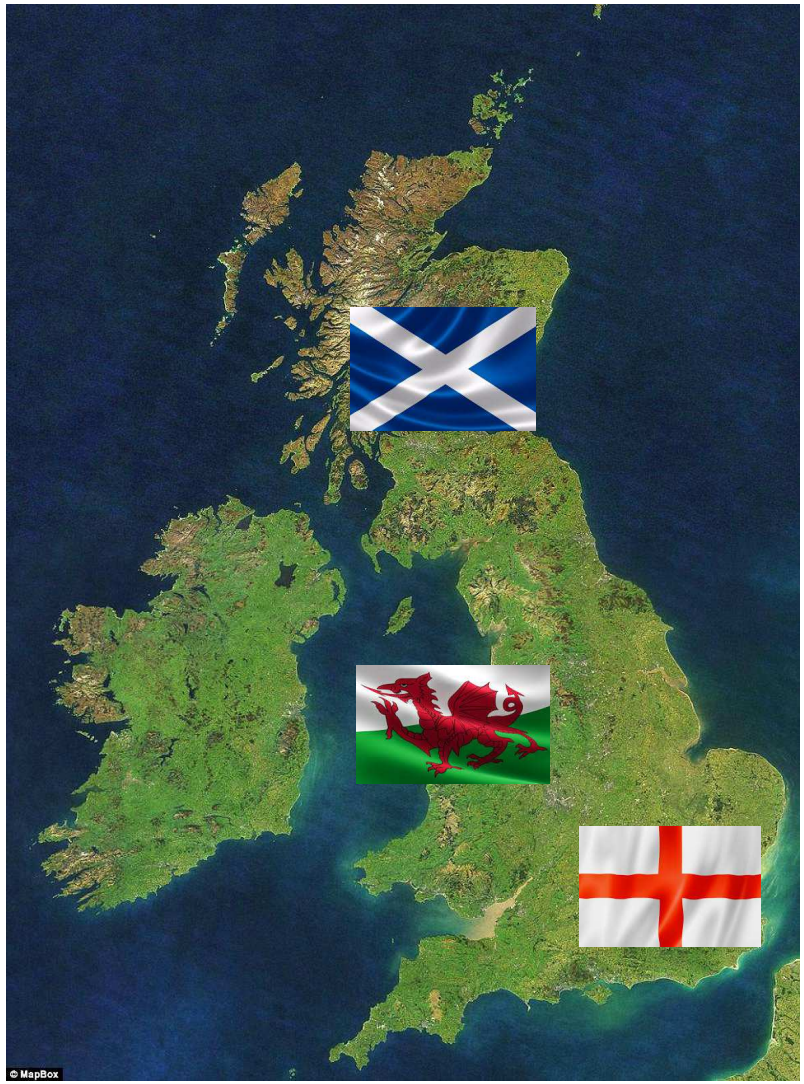
History in the UK

No standardisation across the UK

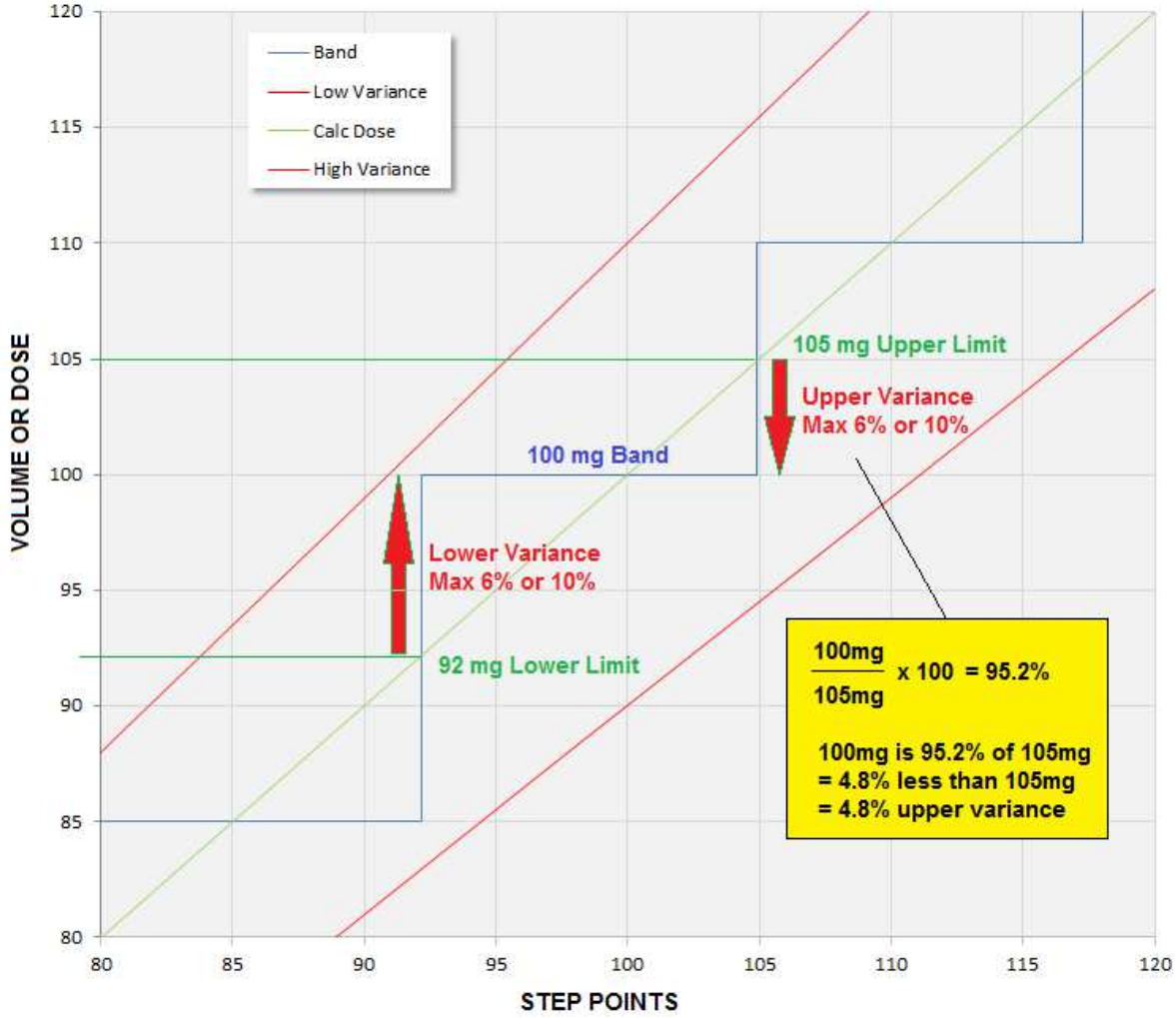
- Scotland and Wales each had own models
- England had multiple models

2011 Burhan Zavery introduced logarithmic dose banding with 5% variance limits

- Easy 20% dose reduction - one of the few benefits
- Other dose reductions difficult (e.g. 33%)
- Doses difficult to measure (e.g. 723.5mg)
- Poor uptake



Variance Limits and Terms



100mg dose band ranges from 92-105mg “calculated doses” (or step points)

Using the example in the yellow box…

100mg is 4.8% less than the 105mg calculated dose the patient *would* have otherwise received

This is the UPPER VARIANCE for *this* band

Actual variances don’t usually reach the max upper and lower red lines due to rounding.

A new standard

Working group in Manchester (Jan 2016) with pharmacists from:

- 2 cancer hopsitals (Marsden & Christie),
- 1 district general hospital (Durham & Darlington),
- 1 large teaching hospital (Sheffield)
- Also immunotherapy pharmacokinetics with Kayode from Christie

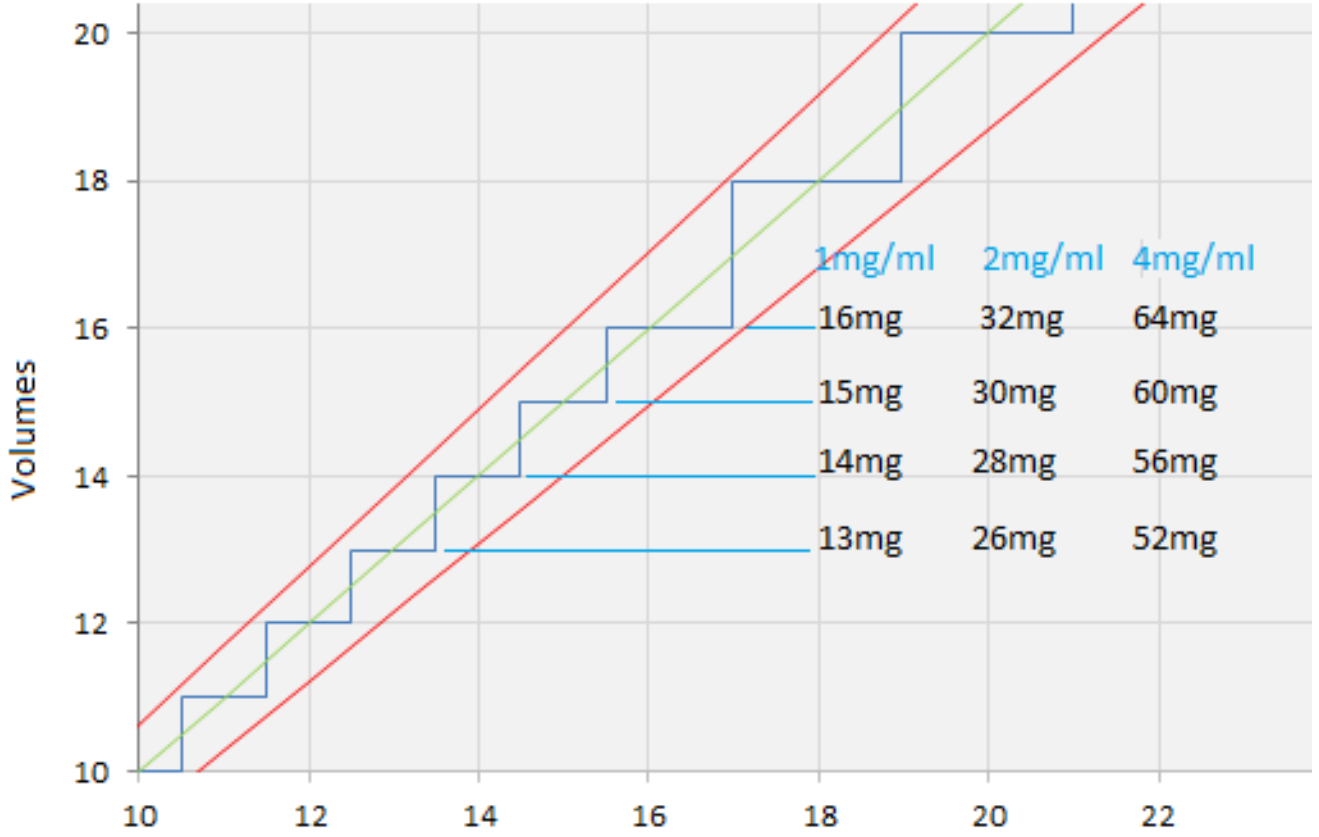
- Three types of dose banding were created using either 6% or 10% variance:
  - Attenuated logarithmic (basic standard for low cost drugs)
  - High cost drugs (rounded to nearest vial sizes or fractions)
  - Multiple syringe method ('pick and mix') for syringe pumps
- Note it is the doses that are banded

  how you get to the doses *does not matter* (i.e. mg/m^2, mg/kg, or AUC)

Principles

1. Cytotoxics & conjugates – max 6% variance (from log values)
2. Dose reductions of ~20% by dropping 2 or more bands
3. Doses measurable in one syringe (max 85% capacity of syringe)
4. All drugs of the same conc. have same doses (unless expensive), multiple tables needed if mutliple strengths available (e.g. gemcitabine)
5. Reduced number of bands (inventory) where possible
6. Multiple container doses never >1 more than the absolute minimum possible
7. High cost drugs rounded to neared vial sizes or fractions (half, third, quarter)
8. Break points using the square root of the two bands being evaluated
9. Max dose also banded

Volume Based Tables



Implementation…

Implantación…

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Stakeholder Discussions

Discussions were had with the following:

NHS Clinical Reference Groups (CRGs) – clinicians, experts, commissioners, patients who advise the NHS how services should be provided.

- Medicines Optimisation CRG – Dose standardisation group created here!
- Cancer CRG

Other groups: BOPA (oncology pharmacists), UKONS (nurses), PASG (aseptic group), Royal College of Physicians

Manufacturing: Don't forget the drug companies!

Hold forums and meetings to address concerns, and technical issues

CQUINS & Training

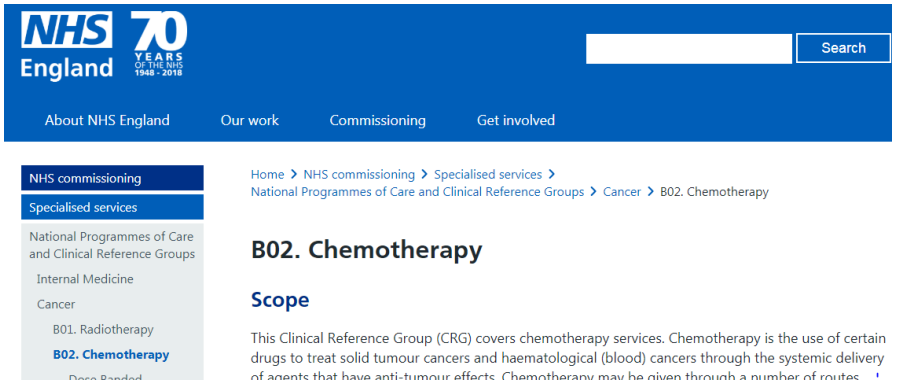
Dose Standardisation Group then organised the following:

- CQUIN – Commissioning for Quality and Innovation – a proportion of hospital income dependant on demonstrating improvements in CQUIN Targets – a Dose Banding CQUIN was created – now into year 3: 90% of chemo doses must match the standard NHS bands to receive payment (based on drug cost)
- National training days – talks from various experts in dose banding, manufacturing, clinical evidence and trials – attended by…
    - Pharmacists
    - Clinicians
    - Manufacturers
    - Commissioners

Maintenance (New Drugs)

The Dose Standardisation Group met with members of the National Institute for Clinical Excellence (NICE)

- New drug reviews and approvals for treatment in the NHS
- Banding tables produced as part of the review process
- Published on the NHS England website
- https://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-b/b02/



Manufacturing Issues

It's not just the doses that need to be standardised –
PRODUCT PRESENTATIONS NEED TO BE FIXED AS WELL

Aspects to consider:

- Infusion fluid type (e.g. glucose, saline) and volume
- Variable volume drugs (e.g. etoposide, oxaliplatin, paclitaxel) where limits often vary from hospital to hospital

Oxaliplatin	0mg – 100mg	250mL
	100.01mg and above	500mL
Paclitaxel	0mg - 79.9999mg	100mL
	80mg - 299.9999mg	250mL
	300mg – 600mg	500mL

- Storage conditions (protect from light, refrigerate)
- Expiry (best before, use by, do not use after)

If we are all using EXACTLY the same product we can purchase together

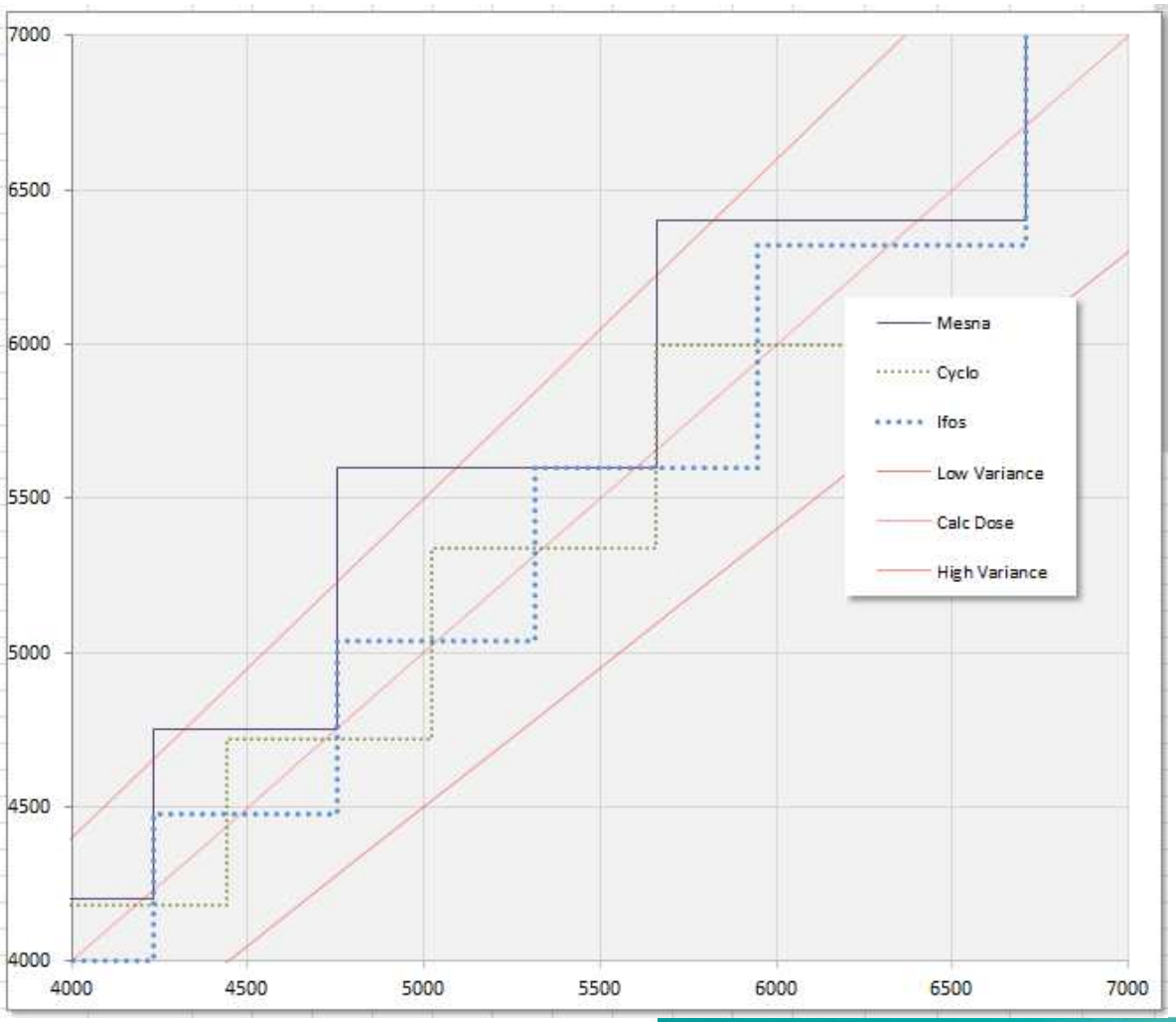
Other problems & solutions

Gemcitabine – licenced dose bands became available, BUT the volumes varied by dose – uptake could have been better (manufacturing based on diluted stock solution of 10mg/mL)

Gemcitabine – available as 38mg/mL and 100mg/mL vials.
Needs 2 separate banding tables.
No easy answer if you use both strengths in one hospital unit.
Methotrexate and cytarabine also pose similar problems.

5-FU - available in 2 strengths 25mg/mL and 50mg/mL – base the dose banding table on 50mg/mL and double the volume to get 25mg/mL doses (doubling a volume will usually still give you a measurable figure – but halving a volume may not)

What to do with mesna



Cyclo and ifos have different concentrations and different bands

Overlay both on the *same* graph and rest the mesna bands on top

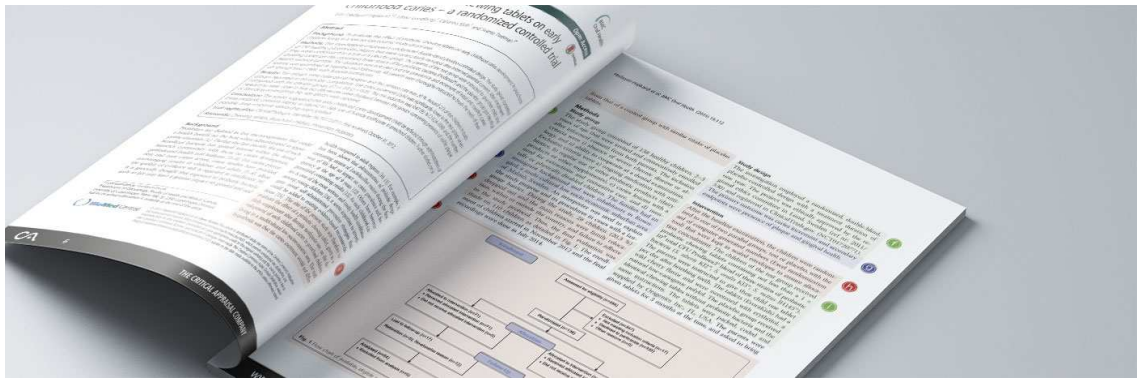
Variance limits breached because of this – but mesna is not toxic

Evidence

Is dose banding having any clinical effect on cancer treatment?

More and more papers are being published in support of dose banding…

- Standard chemotherapy
- Monoclonal antibodies
- Paediatrics (children appear to have no ill effects, but infants require more data)



Standard Chemotherapy

The Clinical Impact of Dose-Banding (GJ Sewell, 2006)

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

Dose banding as an alternative to body surface area-based dosing of chemotherapeutic agents (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 the handling of drugs provided more AUC variance than anything that dose banding would do

Monoclonal Antibodies/Biologics

Fixed Dosing of Monoclonal Antibodies in Oncology (JJMA Hendrikx, 2017)

- 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

(this is larger than for standard chemotherapy – but still very conserative)

10% *does not* apply to conjugates where there is a standard chemotherapy agent attached to a biological carrirer – keep to 6% variance here

Monoclonal Antibodies/Biologics

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 weight effect on clearance[b]	Proposed fixed dose	Corresponding body size based dose after fixed dosing	References
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	40–140 kg: 600 mg, 2 weekly	4.2–15 mg/kg	[33, 36, 37]
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.*					*Approved fixed dose*		[19, 20]
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	1.3–2.2 m^2: 500 mg, weekly (with 800 mg loading dose)	227–384 mg/m^2 (364–615 mg/m^2 loading dose)	[34, 35, 38]
Ipilimumab	3 mg/kg; 3 weekly	3–10 mg/kg	4.15	0.708	0.360	0.642	40–60 kg: 150 mg, 3 weekly 60–100 kg: 250 mg, 3 weekly 100–140 kg: 350 mg, 3 weekly	2.5–3.8 mg/kg 2.5–4.2 mg/kg 2.5–3.5 mg/kg	[57–59]
Nivolumab	3 mg/kg; 2 weekly	1–10 mg/kg	8.0	0.580	0.228	0.707	40–140 kg: 240 mg, 2 weekly	1.7–6 mg/kg	[44, 60]
Obinutuzumab	1,000 mg per cycle (cycle 2–6)	1,000–2,000 mg	2.76	0.383	0.083	0.231	*Approved fixed dose*		[61–63]
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	*Approved fixed dose*		[64–66]
Panitumumab	6 mg/kg; 2 weekly	2.5–9 mg/kg	3.66	0.526	0.269	0.411	40–80 kg: 300 mg, 2 weekly 80–140 kg: 500 mg, 2 weekly	3.75–7.5 mg/kg 3.5–6.25mg/kg	[67–69]
Pembrolizumab	2 mg/kg; 3 weekly	1–10 mg/kg	8.1	0.489	0.23	0.595	40–140 kg: 150 mg, 3 weekly	1.1–3.8 mg/kg	[49, 70, 71]
Pertuzumab	420 mg; 3 weekly (840 mg loading dose)	420–1,050 mg	3.07	0.747	0.239	0.516–0.589	*Approved fixed dose*		[72–75]
Ramucirumab	8 mg/kg; 2 weekly	8–10 mg/kg	5.5	Not reported	0.336	Not reported	*Insufficient data*		[56, 76]
Rituximab	375 mg/m^2; interval is variable	375–2,250 mg	2.98	0.73	0.257	1.02	1.3–2.2 m^2: 800 mg per administration	364–615 mg/m^2	[39, 40, 77]
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	40–140 kg: 450 mg, 3 weekly	3.2–11.3 mg/kg	[13, 41–43, 78]

Fixed dose is proposed if the effect of body weight on the volume of distribution and clearance is minimal (<0.5). If the effect of body weight is strong (>0.5) or unknown and a wide therapeutic window is 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 tested) dose after single administration.

[b]The effect is presented as the exponent used in population pharmacokinetics models in formula 1 to correct for the effect of body weight, whereas 0 is used for no effect and 1 is used for a linear effect.

Abbreviations: BSA, body surface area; EMA, European Medicines Agency; CLL, chronic lymphocytic leukemia.

Paediatrics

Investigating the potential impact of dose banding for systemic anti-cancer therapy in the paediatric setting based on pharmacokinetic evidence (M White-Koning et al, 2017)

- Tested dactinomycin, busulfan, carboplatin, cyclophosphamide and etoposide
- Compared calcuated dose AUC with NHS England dose bands
- No statistical difference seen

Some benefits of dose banding will not be seen in paediatrics

- Low use of most drug doses – wider spread of dose inventory
- Different volume sizes required in smaller patients – non standard volumes

Summary

- Created a system based on attenuated logarithmic banding
- Engaged with relevant professions for approval (sought evidence)
- Promoted and financially encouraged by the NHS
- Created a longer term maintenance system with NICE
- Started buying and manufacturing in batches