National Cancer Control Programme

Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

NCCP GUIDANCE DOCUMENT

DOSE BANDING FOR SYSTEMIC ANTICANCER THERAPY (SACT)

Version	Date	Amendment	Approved By
1	03/06/16	Version 1	Working Group
2	23/08/19	Document reviewed to: 1. Amend MOCIS to NCIS following rebranding 2. Update references to dose banding in NCIS 3. Include updated NCRI statistics on estimated SACT usage in background 4. Include additional drugs now added to the national dose band tables in section 5.2	Working Group

Table of Contents

Acknowledgements

The NCCP would like to thank the members of the Working Group involved in developing and approving this Guidance document as well as the following organisations and individuals:

- Mark Parsons, Scottish Oncology Pharmacy Practice Group
- Richard Nuttall, NHS England
- Northern England Strategic Clinical Networks
- British Oncology Pharmacy Association
- Gail Povey, South West Wales Cancer Centre

1 Background

The use of Systemic Anti-Cancer Therapy (SACT) has risen significantly in recent years, with an increase of 39% noted between 1994-2004 in Ireland.[1]. This use is expected to continue to increase by ~50% by 2025.[2] A report published by the National Cancer Registry in April 2019 estimates that the number of patients receiving SACT for the treatment of their cancer will increase by an average of 70% between 2015 and 2045.[3] While this has brought undoubted benefits to patients, it also presents a challenge to patient safety as the number of SACT drugs expands and the use of oral SACT increases.

As a result of the increasing population of cancer patients and the treatment options available to these patients, pharmacy aseptic compounding units are experiencing corresponding rises in workload. Contributing factors include; the use of new agents, new treatment developments with established SACT (such as use of weekly infusions SACT schedules in combination with newer agents, to decrease toxicity and increase effectiveness of treatment) and the emergence of early access programmes with their associated documentation requirements.

Dose banding is a pragmatic approach to dose selection of SACT agents. It is a tool to rationalise SACT services in order to meet the growing demand for increasingly complex SACT using finite resources. Dose banding has being utilised in hospitals in England, Wales, Scotland and Northern Ireland for a number of years.[4-6] An increase in the range of products available from licensed manufacturing units with extended shelf lives has meant an increased opportunity for hospitals to purchase in readymade products.

The NCCP recognised that there was a need to develop a Dose Banding Guidance in order to:

- Have agreed national dose banding tables in place
- Address service demand
- Expand the number of drugs that are included in the national dose banding tables
- Aid in the management of increasing workload within hospital pharmacy aseptic compounding units
- Further expand the opportunity to purchase ready made products

The NCCP recommend dose banding as a strategy to manage SACT capacity. This approach has been agreed at a national level by the Irish Society of Medical Oncology (ISMO) and the Irish Haematology Society (IHS).

The aim of these documents is to support a framework for dose banding to be applied locally. The implementation of dose banding is not mandatory but where dose banding is introduced, the national dose banding tables should be utilised. The dose banding recommendations are intended for use by sites that choose to adopt them in order to assist capacity issues, improve efficiencies and to standardise and streamline prescribing at their site. A series of dose banding tables have been developed in line with this Guidance document. All or part of these tables may be adopted for use at your site as deemed applicable to your local practice.

Dose banding of SACT has already being implemented in a number of Irish hospitals.[7] Over 30 Dose Banding Tables have been prepared by the NCCP. Hospitals should incorporate the national dose bands into their local practice, as appropriate to their service, to facilitate standardisation of prescribing across the health service.

In April 2016, the draft documents and dose banding tables were circulated to key stakeholders as part of a national consultation exercise. All feedback was considered by the group. The dose banding documents were approved following consultation in 2016.

1.1 What is Dose Banding

A system whereby, through agreement, doses of SACT drugs calculated on an individualised basis, that are within defined ranges or bands are rounded up or down to predetermined standard doses.[8] The maximum variation of the adjustment between the standard dose and the doses constituting each band is typically 5% or less. A range of syringes or infusions manufactured by pharmacy aseptic compounding unit staff or purchased from licensed manufacturers, can be used to administer the standard dose.

1.2 Aims and Objectives of the Dose Banding Working Group

A working group of the NCCP was formed to undertake this work in 2016 with pharmacist representation from hospital pharmacy aseptic compounding units as well as hospitals that outsource to external manufacturing units.
The aim of this group was to develop dose banding guidance documentation and tables through a process of consultation and consensus.

The working group were responsible for:

- Developing guidance documents to facilitate the introduction of dose banding in Irish hospitals.
- Developing a communication plan for the introduction of dose banding in Irish public hospitals.
- Identifying drugs and regimens suitable for dose banding.
- Developing single nationally approved dose bands for chemotherapeutic agents.
- Developing dose banded variance tables to validate dose bands.

- National agreement of dose banding variance limits for both SACT including monoclonal antibodies was sought through consultation with ISMO and IHS.

- Agreement on the most appropriate methodology for dose banding was reached prior to development and implementation of dose bands.

- Agreed dose bands were required to be practical for both commercial and hospital pharmacy aseptic unit preparation work, operating within a minimum of manual manipulations, for both bolus and infusion dose bands.

2 Benefits and Limitations of Dose Banding

2.1 Benefits of Dose Banding

- Dose rationalisation
- Potential improved availability of items as stock
- Potential for reduction in patient waiting time
- Potential for improved pharmacy capacity for SACT
- Potential for better value when outsourcing
- Potential reduction of medicine waste by:
  - ability to re-assign dose banded doses if administration is cancelled.
- Standardised national implementation of dose banding will ensure consistency across hospitals thus minimising risks when staff move between different hospitals
- Standardised national implementation of dose banding will be included in the National Clinical Information System (NCIS)

2.2 Limitations of Dose Banding

- Correct stock utilisation including expiry date is required to minimise the risk of wastage
- Dose banded products purchased from an external compounding supplier are unlicensed products. Local procedure for dealing with unlicensed products with regard to batch tracking and recording should be followed
- Where multiple syringes are used to administer a single dose, correct labelling of the products and training of staff administering the dose is essential
- Clinical trials may not always permit dose banding

3 Accuracy of Dose Banding

SACT dosing based upon BSA (Body Surface Area) is already subject to a number of limitations in terms of accuracy [5,9]

- BSA is estimated by formulae not measured
- BSA formulae take no account of obesity or cachexia
- There is no precise correlation between drug clearance and BSA
- Different BSA formulae give different results
- The most popular nomogram for BSA calculation is DuBois which is based on only 9 subjects [10]

Rounding usually occurs during calculation of BSA and calculation of dose to be administered as mg/m^2 due to limitations with regard to the nearest measurable volume in a syringe or solid dosage form.

Dose banding does not add significantly to the level of imprecision inherent in BSA-based dose calculations nor significantly alter the dose-density of SACT administered over a treatment course. The quantifiable service and patient benefits achieved by banding outweighs any theoretical disadvantages.[9]
The use of banding to give doses within ±5% (and beyond in certain instances) of the prescribed dose has been demonstrated to be acceptable in practice in Scotland and in many sites in the NHS.[4-6] Many clinical trials now allow dose banding providing the 5% rule is maintained.

4 Situations Where Dose Banding is Not Recommended

4.1 Paediatrics

Dose banding is not prohibited in paediatrics but the advice of specialists within Paediatric Oncology and Haematology must be sought if considering dose banding. It is rarely used for a number of reasons. Paediatrics are not included in this document.

4.2 Cachexia and Obesity

The ASCO clinical practice guideline on appropriate chemotherapy dosing for obese adult patients with cancer recommends that full weight–based cytotoxic chemotherapy doses be used, particularly when the goal of treatment is curative. Clinicians should respond to all treatment-related toxicities in obese patients in the same ways they do for non-obese patients.[11]

4.3 Clinical Trials

Dose banding can be used in clinical trials with prior agreement of the trial principal investigator and sponsor. Discussions regarding the use of dose banded products should take place locally at the trial feasibility meeting or at the Site Initiation Visit in order for approval to be gained from the trial sponsor.

4.4 Other

In certain cases, where there are clinical reasons for an individual patient not to be dose banded, an individualised dose calculation may be preferred– decision over dosing to be made locally in consultation with treating consultant. The consultant should write "**NOT FOR DOSE BANDING**" clearly on the prescription, along with their signature and date or as detailed in the local SOP governing dose banding. The rationale for this should be documented by the consultant as outlined in the local SOP.

5 Drug and Dose Volumes Suitable for Dose Banding

The essential determinants for suitability for dose banding are outlined below:

5.1 Drugs

- The requirement to dose band to ensure the cost effective use of vial sizes for high cost drugs such as monoclonal antibodies.
- Oral SACT due to the constraints of the solid dose presentations.
    - Where there is only one strength of a drug available, there is no requirement for dose banding as the dose prescribed must be accommodated within dose rounding to the strength available e.g. chlorambucil 2mg. Where a drug has more than one strength available, dose banding can be considered as a means to ensure the dose being prescribed is possible to be dispensed (within a dispensing system such as NCIS) e.g. capecitabine is available as 500mg, 300mg and 150mg tablets.

5.2 Dose Volumes

- All dose bands will be required to be compatible with agreed dose measurement limits for doses to be prepared accurately within aseptic units.

- Agreed measurement limits were:
    - <1ml drug volume rounded to nearest 0.01ml
    - 1 to 3ml drug volume rounded to nearest 0.1ml
    - 3 to 10ml drug volume rounded to nearest 0.2ml
    - >10ml drug volume rounded to nearest 1ml

- The number of syringes available for use within each dose band will be minimised where possible, to maximise stock rotation and management efficiency. The syringe numbers were confirmed within each cancer centre to ensure they met local requirements and working practices.

- Volumes in syringes up to 50ml would be acceptable for use in the dose bands for centres who would wish to use them in syringe administration devices.

SACT agents that meet above requirements and are high usage items can be considered for dose banding. Examples of drugs include:

- 5-Fluorouracil infusors
- 5-Fluorouracil syringes
- Azacitidine injections
- Bendamustine infusions
- Bortezomib injections
- Carfilzomib infusions
- Carboplatin infusions
- Cisplatin infusions
- Cyclophosphamide syringes/ infusions
- Cytarabine infusions
- Dacarbazine infusions
- Docetaxel infusions
- Doxorubicin syringes
- Epirubicin syringes
- Etoposide infusions
- Gemcitabine infusions
- Irinotecan infusions
- Methotrexate infusions
- Mitomycin injections
- Nab-Paclitaxel infusions
- Oxaliplatin infusions
- Paclitaxel infusions
- Pemetrexed infusions
- Vinorelbine infusions

Examples of high cost drugs include monoclonal antibodies (mAbs) of which the following have been deemed suitable for dose banding.

- Bevacizumab
- Cetuximab
- Daratumumab
- Ipilimumab
- Trastuzumab
- Rituximab

Capecitabine has been deemed suitable for dose banding due to the requirement to combine different tablet strengths to administer the prescribed dose.

The list outlined above is not exhaustive. Not all SACT drugs meet the requirements indicated above. Dose banding may be extended to include other drugs at a later point.

The dose banding Guidance Document will be reviewed as required based on feedback or updated evidence. The FAQs and the dose banding tables will be updated as required e.g. when new drugs are to be included.

6 Choice of Dose Banding Scheme

Currently there is no standardised method of assigning dose bands internationally. All are based on a number of common principles.

The main determinants of dose bands are:

- dose/m^2
- limits of variance from the calculated dose (±5%)
- strength of the drug formulation (mg/ml)
- agreed maximum number of syringes per dose
- maximum fill-volume per syringe or other physical constraints inherent in delivery devices for fixed duration infusions.

6.1 Schemes for Assigning Dose Bands

There are a number of schemes for assigning dose bands:

6.1.1 BSA Based Banding

Bands are set in increments of body surface area. The patient's body surface area is rounded up or down to one decimal place and a set dose band given for that BSA e.g. doxorubicin 60mg/m^2 for patient of 1.82 m^2, the BSA is rounded to 1.8m^2 and a dose of 110mg given.

6.1.2 Target Dose Banding or Drug Centred Dose Banding

The patient's dose is prescribed as per BSA and then rounded up or down to the nearest band e.g. doxorubicin 60mg/m^2 for patient of 1.82 m^2, the calculated dose is 109.2mg. This would then fall into a pre-designated band e.g. 105mg to 114mg for which a dose of 110mg is given.

6.1.3 Logarithmic Dose Banding

The 'Logarithmic dose-banding' (LDB) approach to SACT dose banding has been devised by Geoff Hall, Senior Lecturer, Medical Oncology, St James's Institute of Oncology, Leeds. This works by logarithmically increasing dose bands by a set percentage working to an approximate 5% variance on a range of drugs. The proposed dose banding principle being applied with this attenuated LDB approach is such that no patient will receive a dose less than 95% of that originally prescribed but some may receive slightly more than 105% to ensure no under-dosing of patients.

It is acknowledged that there is little difference to the final dose whichever of these methods is used.[5,12]

The "Target Dose Banding" has been chosen for the NCCP national dose-banding tables.

The reasons for choosing this scheme are:

- No need to create specific dose banding tables for each regimen.
- Easier to maintain bands.
- Consistency across regimens.
- Dose modifications are more transparent and straightforward.
- Less risk of a 20% dose reduction being lost or obscured by an upward banding decision.
- It is only necessary to input the dose band for each drug into a dispensing system on a single occasion. That band could be used for all banded regimens irrespective of the dose per m^2 without the need for additional manual manipulation.

6.2 Validation of the Dose Bands Chosen

The NCCP has prepared a dose banded variance table to validate the dose bands; this calculates the range of variance from the original intended dose. A 5% variance has been agreed with ISMO and IHS. Dose banding variance tables have been completed for each drug recommended for dose banding and the table demonstrates that the 5% rule is intact for the most commonly used doses of cytotoxic agents.

- There is a degree of uncertainty around the dosing of monoclonal antibodies and in many clinical circumstances, doses are fixed without any adjustment for BSA or weight. The variance for monoclonal antibodies has been extended slightly beyond 5% .[13]
- For some of the dose band tables constructed, there are variances of up to 9.5%. These are to accommodate dose rounding of doses at the lower end of the tables in order to facilitate the nearest measurable quantity. This is for dose rounding as opposed to dose banding.
- Where doses have extended beyond 5%, the table is highlighted in red to indicate that the variance is greater than 5%.

The variance tables cover a broad range of doses, not all of which would be suitable to be kept as stock. Individual sites should identify their own high usage items and doses with a view to maintaining stock levels of those items to enhance throughput.
Dose banding may be constrained by limits within electronic prescribing systems. These constraints should be addressed locally. The National Dose bands have been built in NCIS as selectable strengths of products.

Please note that as NCIS suggests the dose with the least variance rather than referring directly to the national dose banding tables, the suggested NCIS dose may differ from the recommended dose band. It is a local decision whether or not to accept NCIS prompts or to manually change the NCIS dose band to follow the national dose banding tables.

6.3 Dose Adjustments and Dose Reductions for Banded Doses

When the dose of a dose banded product is reduced, e.g. For toxicity, there are a number of approaches to changing the dose:

1. Apply the dose adjustment to the original mg/m^2 prescribed dose, recalculate the dose and then apply the nearest dose band
2. Apply the percentage dose reduction to the original intended calculation dose, before the dose banding, recalculate the drug dose and then apply the dose band
3. Apply the percentage dose reduction to the banded dose, recalculate and select the new dose band

The method to be used should be defined locally and detailed in the SOP governing dose banding.
NCIS applies dose reductions to the original dose, this can be applied as a percentage of that dose, as a dose per m^2 or kg or the dose may be selected from the dose band table.

7 Procedure for Use of Dose Banding

1. For the purpose of dose banding the patient's total dose should be calculated and then matched to a range in the appropriate table, e.g. if BSA 1.76m^2, for paclitaxel 80mg/m^2, dose calculates to 141mg. This falls into to 139-150mg bracket and so the dose banded dose to be administered is 144mg.

2. If doses on prescriptions are not already banded by the prescriber[1] the pharmacist or nurse undertaking validation of the SACT prescription may amend the prescription according to the agreed dose bands given in the associated dose banding tables.

3. The pharmacist or nurse[2] will endorse any amendments to original prescription, e.g. doses rounded for dose banding, with the date and their initials. Details of how this

[1] The local SACT prescribing policy should include reference to the use of dose banding
[2] The local SACT prescribing policy should include the agreement with regard to staff who may amend prescriptions for the purpose of dose banding.

is to be done should be defined locally and detailed in the local SOP governing dose banding.

4. When a new national dose-banding table is agreed all patients should change to the dose-banded dose at the next available opportunity, avoiding wastage of any product already compounded.

5. Drugs will be supplied to the ward/ day centre as pre-filled syringes (or combinations of pre-filled syringes), infusion devices (e.g. infusors)/infusion bags or tablets for administration. Doses in syringes may be supplied as a combination of 2 to 3 syringes each containing a proportion of the total dose. Each syringe will need to be labelled with the amount of drug it contains as well as other labelling requirements detailed the NCCP Oncology Medication Safety Review Report Appendix 10 (Link). Infusors/infusions will be supplied as a single infusor/bag containing the full dose banded dose.

Example: If patients requires a dose of doxorubicin= 120mg, a 100mg/50ml syringe and a 20mg/10ml syringe could be supplied

6. Where multiple syringes are supplied to administer a single dose, ideally no more than 3 syringes should be supplied per dose. However, nursing staff may prefer to give smaller volume syringes and so, there may be occasions where it is preferable to give more than three syringes for one dose. This practice of using multiple syringes to administer a single dose, where adopted by sites, should be detailed in the local SOP governing dose banding.

Example: Doxorubicin 160mg, a 100mg/50ml, 30mg/15ml x 2 would be supplied but nurses may prefer to give 2 x 50mg/25ml, and 2 x 30mg/10ml.

7. Dose banded OAM prescriptions can be amended by the hospital pharmacist or nurse. Any amendments made to the original prescription will need to be counter-signed by a clinician prior to dispensing in a pharmacy.[14]

8. Pharmacy departments issuing dose banded products must ensure that they are labelled in accordance with the labelling details contained in the NCCP Oncology Medication Safety Review Report Appendix 10 (Link). This applies to products prepared internally as well as products that have been purchased from an external compounding service.

The dose-banded drugs are issued to the ward/day centre for administration in the usual fashion.

8 References

1. NCCP. NCCP Oncology Medication Safety Review Report. 2014.
2. National Cancer Registry. Cancer projections for Ireland 2015 2040. National Cancer Registry. Cork, 2014 Available at: https://www.ncri.ie/sites/ncri/files/pubs/Cancer%20projections%20for%20Ireland%202015%20-%202040.pdf
3. National Cancer Registry (2019) Cancer incidence projections for Ireland 2020-2045. National Cancer Registry, Cork.. Accessed 08/05/19. Available at: https://www.ncri.ie/sites/ncri/files/pubs/CancerIncidenceProjections_NCRI_fullreport_09042019_final.pdf
4. NICE Chemotherapy dose standardisation. Accessed 02-May-19, available at https://www.nice.org.uk/advice/ktt22/chapter/Evidence-context
5. Gillian A. BOPA Toolkit: How to Implement Dose Banding of Chemotherapy. Network Pharmacist (NELCN) on behalf of Network Cancer Pharmacists. 2008.
6. SOPPG. Guidelines for Dose Banding of Systemic Anti-Cancer Therapy Development and Governance Framework. 2015.
7. O'Leary CE, Collins A, Henman MC, King F. Introduction of a dose-banding system for parenteral chemotherapy on a haematology-oncology day ward. J Oncol Pharm Pract. 2019 Mar;25(2):351-361. doi: 10.1177/1078155217736376. Epub 2017 Oct 23.
8. Plumridge R, GJ S. Dose Banding of cytotoxic drugs:A new concept in cancer chemotherapy. Am J Health-Syst Pharm. 2001;58(Sep 15).
9. Ratain M. Body Surface Area as a basis for dosing of anti-cancer agents: science, myth or habit. J Clin Oncol. 1998;16(2297-9).
10. Shuter B, Aslani A. Body surface area: Du Bois and Du Bois revisited. European Journal of Applied Physiology. 2000;82(3):250-4.
11. Griggs JJ, Mangu PB, Anderson H, Balaban EP, Dignam JJ, Hryniuk WM, et al. Appropriate Chemotherapy Dosing for Obese Adult Patients With Cancer: American Society of Clinical Oncology Clinical Practice Guideline. Journal of Clinical Oncology. 2012;30(13):1553-61.
12. Williamson S, Polwart C. Guidelines for the Dose Banding of Cancer Chemotherapy. NECN.Vers 1.4.
13. Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol. 2009;49(9):1012-24.
14. Medicinal Products (Prescription and Control of Supply) Regulations (SI 540/2003), (2003).