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Dose-banding of cancer chemotherapy

Dose-banding enables the timely provision of outpatient chemotherapy, improved workload management and prospective QC of cytotoxic doses

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Doses of cancer chemotherapy are normally based on patient body surface area (BSA) or, in the case of carboplatin, patient renal function and pre-defined pharmacokinetic target values. This approach requires that 'bespoke' chemotherapy infusions are prepared for each individual patient. In most cases, chemotherapy is administered in the outpatient setting, and the evaluation of blood counts and renal and hepatic function along with other indicators of the patient's clinical status, precludes the preparation of infusions in advance of the patient's visit. Timely provision of chemotherapy to oncology outpatient clinics is therefore a constant challenge for hospital pharmacy aseptic units. This situation creates stress for oncology outpatients and for pharmacy and nursing staff involved in the process of providing and administering chemotherapy. Such delays can also result in increased pharmacy and nursing overtime costs and the non-availability of specialist staff if delays cause administration of chemotherapy to extend beyond normal working hours.

In recent years the scientific validity of traditional individualised dosing algorithms has been questioned.^{1,2} The realisation that some flexibility of chemotherapy dosing is possible has been combined with the advantages of batch-preparation of chemotherapy in a new approach called 'dose-banding'. Dose-banding is a system where prescribed doses (calculated according to BSA) are fitted to pre-defined dose ranges or 'bands'. For each band a standard dose is given (usually the mid-point of the lower and upper dose limits of the band). The standard dose is provided with a limited range of pre-made infusions or pre-filled syringes, used singly or in combination. Plumridge and Sewell³ defined dose-banding as: "A system where chemotherapy doses, calculated by BSA or other means, are fitted to pre-defined dose ranges or 'bands'. For each band a standard dose (mid-point of band) is provided with standard, pre-made syringes or infusion bags used singly or in combination. These can be prepared by the hospital pharmacy, or purchased from a commercial source."

A practical example to illustrate dose-banding is that of 5-fluorouracil (5-FU) given in protocols requiring an IV bolus dose of 600mg/m². A dose-banding scheme has been devised to cover a range of patient BSA values from 0.98–2.02m², using a bandwidth of 50mg and a range of pre-prepared fluorouracil syringes; 50mg, 100mg, 125mg, 250mg, 500mg, 600mg. A part of this scheme, from 875–975mg, is shown in Figure 1. In this schematic, a patient dose calculated (by BSA) as 880mg, would be fitted to

the band from 875–925mg, and the standard dose of 900mg (mid-point of the band) would be given as pre-prepared syringes of 1 x 600mg, 1 x 250mg, 1 x 50mg (three syringes total). Throughout the scheme, the maximum variation of the administered dose from the prescribed dose is <5%. At the time dose-banding was first introduced (1998) this variation was considered acceptable by most prescribers and oncology pharmacists.³

Ideally, the batches of standard 'pre-made' syringes would be assigned a shelf-life of 84 days or more. This is dependent upon validation of chemical, physical and microbiological stability, and the preparation of infusion batches in a licensed facility. The batch preparation of the standard infusion doses also enables the implementation of quality control and end-product testing. Using semi-automatic pumps to produce bulk chemotherapy solutions in large-volume empty TPN bags, it is possible to use rapid methods to assay and identify the drug prior to filling of infusion bags or syringes. If the infusion shelf-life is extended (for example to 84 days) it is also possible to quarantine the batch until microbiological environmental monitoring and sterile media fill data are available for the batch. These attributes add significantly to patient safety and reduce the probability of medication errors. The main advantages of chemotherapy dose-banding are outlined below:

- Timely provision of outpatient chemotherapy.
- Control of workload with 'ready to use' doses:
 - a) inhouse infusion batches of standard doses
 - b) outsourced infusions/pre-filled syringes
 - c) licensed pre-filled syringes/infusions.
- Treatment delays reduced/eliminated.
- Prospective QC and end-product testing.
- Reduced risk of medication errors.
- Drug wastage minimised/eliminated – reduced costs.

The selection and administration of multiple syringes or infusions to give the standard dose for banded chemotherapy must be controlled by authorised protocols. Together with comprehensive staff training, these help ensure that no medication errors are associated with dose-banding schemes. When implementing new dose-banding schemes, it is essential that agreement is achieved between pharmacy, nursing and medical staff. Prior to the introduction of dose-banding, some concerns were expressed about the need to administer multiple syringes or infusions (usually a maximum of three) to provide the standard dose. However, in our experience, this has not been an issue in practice and, with these controls in place, dose-banding has been shown to be remarkably error-free over the first 12 years of use.

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Infusion stability is a key pharmaceutical issue and a prerequisite in the assignment of adequate shelf-lives for the standard, pre-prepared infusions. Dose-banding schemes and infusion stability studies must be carefully designed to ensure that physical and chemical stability is assessed over the appropriate drug concentration range, using the correct container and diluents required for clinical use, and that storage conditions reflect those used in practice. It is essential that all analytical methods are fully validated, eg, drug assays must be stability-indicating. Some infusion stability studies use a 'sequential temperature' design, where the same drug infusions are stored at different temperatures in sequence to replicate the situation where an infusion is removed from refrigerated storage, transported to the ward, and after being held there the infusion is returned to the pharmacy unused (because of an unforeseen delay in the patient's treatment) and refrigerated for later re-issue. Examples of a rigorously designed dose-banding scheme for carboplatin infusions and corresponding stability studies based on the sequential temperature design, are available in the literature.^{4,5} The maintenance of infusion sterility is also critical for infusions subjected to extended periods of storage. Aseptic techniques must be validated for all compounding units preparing such infusions, and extensive quality assurance procedures should be implemented.

Gaining acceptance for dose-banding from prescribers is crucial to the success of this approach. We recently published a UK-wide survey of chemotherapy prescribers, including clinical oncologists, medical oncologists and haematologists.⁶ Validated questionnaires with both quantitative and qualitative elements were mailed to 1,104 prescribers across the UK and 387 responses were received (35%). Many respondents were concerned about delays to outpatient chemotherapy associated with preparation of bespoke infusions, 81% knew about dose-banding and 63% reported chemotherapy dose-banding in their own hospital. Dose-banding was clearly distinguished from dose-rounding in the questionnaire to avoid any confusion between these different systems of dose rationalisation.

There was some difference of opinion concerning the maximum variation from the prescribed dose permitted in dose-banding schemes. Maximum deviations of <5% and <10%, were supported by 52% and 40% of respondents, respectively. There was also support for dose-banding drugs with non-BSA, pharmacologically-based dosing schemes such as carboplatin, and for dose-banding of targeted therapies such as trastuzumab.

Some of the qualitative responses from clinicians highlighted the lack of clinical evidence to support dose-banding and to ensure there was no difference in therapeutic outcomes between individual and banded dosing of chemotherapy. The authors of this article have already addressed this in part with a clinical and pharmacokinetic study on patients receiving 5-FU infusion. This study used a pharmacokinetic end-point (area under the plasma-concentration time-curve [AUC]) to measure the amount of drug available to the tissues as a surrogate for small changes in clinical effect or toxicity. This approach greatly reduced the number of patients required for the study. Analysis of the pharmacokinetic data obtained showed that AUC was not signifi-

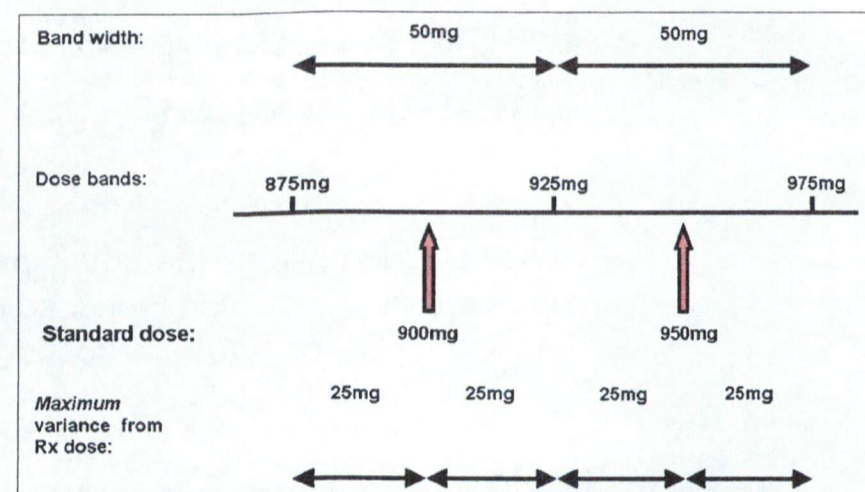


Figure 1. Showing part of the dose-banding scheme for 5-fluorouracil

cantly affected by administering a banded dose in place of an individualised dose.⁷ We expect to report on dose-banding studies for carboplatin, where dose is calculated using a more rigorous pharmacologically-based scheme,⁴ later in the year.

Conclusion

Dose-banding is a simple and practical approach to the management of chemotherapy workload and improving the experience of patients receiving treatment in the oncology outpatient setting. Patient waiting times and drug wastage can be significantly reduced with dose-banding.⁸ As discussed, there are clear quality and safety benefits to be gained through dose-banding, while clinical and pharmacokinetic studies indicate there should be no effect on either therapeutic outcome or toxicity. Significant pharmaceutical input is, however, required in constructing dose-banding schemes and to conduct appropriate stability studies to support extended shelf-lives assigned to standard infusions.

In principle, dose-banding should facilitate the development of licensed standard chemotherapy infusions by the pharmaceutical industry or, alternatively, compounding of standard batches of chemotherapy by commercial 'Specials' aseptic manufacturing units. These developments would help augment the output of hospital pharmacy units and bring the ever-increasing chemotherapy workload under control. Additionally, there is no reason why the dose-banding approach cannot be applied to supportive therapies and to non-cancer treatments such as antibiotic infusions. However, the full benefits of dose-banding will only be realised if the pharmaceutical industry can be encouraged to provide, where stability permits, ready to use infusions in standard doses. This will require a departure from the current tendency of each centre developing its own dose-banding schemes and the adoption of common protocols for national or European use. The number of standard pre-made infusions required for each dose-banding scheme could be reduced if the notional limit for maximum deviation from the prescribed dose was increased from 5% to 10%. We found evidence of some prescriber support for this,⁶ but such developments would require further research to ensure that the clinical effect of chemotherapy is not compromised. ■

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