The impact of logarithmic dose banding of anticancer drugs on pharmacy compounding efficiency at Ghent University Hospital

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ABSTRACT

Background Dose banding (DB) (dose rounding with predetermined variation with prescription) enables in-advance preparation of high-turnover anticancer drugs with potential benefit for pharmacy compounding workflow.

Objectives To analyse the impact of potential situations on the efficiency of DB in the pharmacy (safe and maximum storage), calculate preparation lead times and the potential full-time equivalent (FTE) benefit.

Methods Candidate intravenous anticancer drugs were selected for logarithmic DB according to prescribing frequency, infusion volume and stability (usage data 2015 of the tertiary Ghent University Hospital, Belgium). With a selected DB set already stored, a 2-week time study (April/November 2015) provided lead times (between prescription and transfer) for just-in-time and DB preparations. A ‘maximal’ storage (using all drugs with a relative incidence of ≥2% recurrent monthly prescription) and a ‘safe’ storage scenario (lowest monthly prescribing pattern) were used to calculate the potential future FTE change.

Results Mean lead times for DB storage and just-in-time preparation were 17.1 min (95% CI 13.5 to 21.0) and 26.5 min (23.3 to 29.8). For 21 164 yearly preparations with already 5292 in DB (25%), 11 157 and 6 862 could be batch-produced in advance in a maximum storage and safe storage scenario, respectively. The existing FTE in 2015 of 5.41 could then be reduced to 4.91 and 5.27.

Conclusion Further development of DB could contribute to pharmacy compounding efficiency.

METHODS

The following usage data for all prescribed biological and cytotoxic anticancer drugs (non-paediatric/not clinical trial related) in 2015 were retrieved from the electronic oncology prescribing system (Chemopro 2.0, in-house software) of the Ghent University Hospital, Belgium: international non-proprietary name, dose, final concentration after dilution in a specified solvent and day of preparation. In 2015, LDB of 5-fluorouracil, oxaliplatin, gemcitabine, paclitaxel and rituximab was provided a secured storage of 25 different dose strengths. Simulation of more candidate molecules was carried out to explore the potential future benefit.

First, a 2-week study (two separate weeks in April and November 2015) was performed by the Centre of Service Intelligence of Ghent University (Faculty of Economics and Business Administration) to collect lead times of prescriptions and calculate differences between stored DB and just-in-time preparations.
Lead time was defined as the time between receipt of a prescription and readiness for transfer, reported as mean (min) with 95% CI. It should be noted that several preparations can pass through the system at the same time. Transfer started once the preparation was individually labelled and placed at the supply chain department picking desk (with a 15 min pick-up frequency) or sent through a pneumatic tubing system throughout the hospital.

Selection of candidate molecules eligible for DB was based on a physicochemical stability of at least 7 days (combined data from the literature and manufacturer), the frequency of prescribing and the infusion volume (ie, final concentration). A total number of potential DB molecules was calculated for 2015, estimating future storage. Data are expressed as the number of different DB strengths and the total number of stored DB preparations versus just-in-time preparations. Data are analysed both for 2015 and future storage.

Two future scenarios are presented:

1. A ‘maximum’ storage scenario: all preparations in 2015 were rearranged per band and only stable DB preparations (mid-band-doses) with a relative incidence of at least 2% recurrent monthly prescription were retained. This maximum scenario includes the currently stored LDB molecules chosen based on the same criteria.

2. A ‘safe’ storage scenario using the conditions mentioned in point 1 but further corrected for the lowest prescribing amount within the documented shelf-life and calculated per month. For a product with a stability of, for example, 1 month, only the smallest number prescribed in the previous 12 months was retained.

By combining the time study with future storage possibilities, a difference in pharmacy working hours (FTE) could be estimated between the actual situation and the future forecast. The mean preparation time of a DB batch was incorporated.

RESULTS

In the 2-week study a total of 888 individual prescriptions were analysed of which 94 (10.6%) were stored as DB. The mean lead times for DB storage and just-in-time preparations respectively were 17.3 min (95% CI 13.5 to 21.0) and 26.5 min (23.3 to 29.8).

Of the 39 anticancer drugs (10 monoclonal antibodies (mAbs)/cytokines and 29 cytotoxic agents/diverse antitumoral drugs) 15 IV anticancer drugs had stability data of at least 7 days and monthly preparations: bevacizumab, carboplatin, cisplatin, docetaxel, epirubicin, 5-fluorouracil, gemcitabine, irinotecan, methotrexate, oxaliplatin, paclitaxel, pemetrexed, rituximab, IV trastuzumab and vincristine.

The overall number of anticancer prescriptions in 2015 was 21 164 (approximately 58/day) of which 5292 were already stored as DB (25.0%). According to the simulation 6862 (‘safe’ scenario) up to 11 157 preparations (‘maximum’ scenario) could be batch produced in advance. This entails an expected storage of 32.4% (19/day) to a maximum of 52.7% (31/day) of all daily prescriptions. In total 85 different strengths can be stored with a stability varying between 7 days (vincristine) and 6 months (trastuzumab). An overview is given in table 1.

The mean time of preparation within a DB batch was 0.99 min and 2.56 min for, respectively, one infusion bag and one infusion pump.

Compared with 2015 with 8651.5 (7468.8–9849.8) pharmacy working hours per year or 5.41 FTE, the two scenarios had the following impact: the safe storage scenario required an estimated

<table>
<thead>
<tr>
<th>INN</th>
<th>Situation in 2015 No. of individual prescriptions in 2015 per product (n=21 164)</th>
<th>Real-life storage No. of DB strengths in 2015 (n=25)</th>
<th>Future storage No. of potential DB strengths per year (n=85)</th>
<th>Maximal future storage No. of DB preparations (n=21 164)</th>
<th>Safe future storage No. of DB preparations (n=21 164)</th>
<th>Shelf life under specific conditions in days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bevacizumab</td>
<td>665</td>
<td>0</td>
<td>9</td>
<td>554</td>
<td>333</td>
<td>90†</td>
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<tr>
<td>Carboplatin</td>
<td>1045</td>
<td>0</td>
<td>12</td>
<td>752</td>
<td>368</td>
<td>56†——‡</td>
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<tr>
<td>Cisplatin</td>
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<td>0</td>
<td>7</td>
<td>535</td>
<td>182</td>
<td>28†</td>
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<td>Docetaxel</td>
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<td>144</td>
<td>78</td>
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<td>Epirubicin</td>
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<td>4</td>
<td>373</td>
<td>217</td>
<td>84†</td>
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<td>5-Fluorouracil infusion bag</td>
<td>1957</td>
<td>5</td>
<td>5</td>
<td>949</td>
<td>600</td>
<td>28†</td>
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<tr>
<td>pump</td>
<td>1038</td>
<td>3</td>
<td>6</td>
<td>1466</td>
<td>978</td>
<td></td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>830</td>
<td>5</td>
<td>9</td>
<td>775</td>
<td>465</td>
<td>84†</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>691</td>
<td>0</td>
<td>5</td>
<td>494</td>
<td>273</td>
<td>28†</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>1108</td>
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<td>521</td>
<td>384</td>
<td>56†</td>
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<tr>
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<td>5</td>
<td>537</td>
<td>286</td>
<td>14†</td>
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<tr>
<td>Paclitaxel</td>
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<td>5</td>
<td>6</td>
<td>1926</td>
<td>1069</td>
<td>14†</td>
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<tr>
<td>Pemetrexed</td>
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<td>0</td>
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<td>31†</td>
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<tr>
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<td>3</td>
<td>5</td>
<td>552</td>
<td>348</td>
<td>90†</td>
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<tr>
<td>Trastuzumab</td>
<td>1089</td>
<td>0</td>
<td>4</td>
<td>1019</td>
<td>920</td>
<td>180†</td>
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<tr>
<td>Vincristine</td>
<td>934</td>
<td>0</td>
<td>1</td>
<td>427</td>
<td>313</td>
<td>7†</td>
</tr>
<tr>
<td>Summation DB, n (% of all individual prescriptions)</td>
<td>5292 (25.0)</td>
<td>NA</td>
<td>NA</td>
<td>11 157 (52.7)</td>
<td>6862 (32.4)</td>
<td></td>
</tr>
<tr>
<td>Summation preparations NOT DB, n (% of all individual prescriptions)</td>
<td>15 872 (75.0)</td>
<td>NA</td>
<td>NA</td>
<td>10 007 (47.3)</td>
<td>14 302 (67.6)</td>
<td></td>
</tr>
</tbody>
</table>

*Data obtained from manufacturer.

DB, dose band; INN, International non-proprietary name; NA, not applicable.
This study indicates a potential change of LDB on the pharmacy organisation, with an estimated average yearly reduction of 0.5 FTE when the maximal potential storage scenario is compared with the situation in 2015. However, we believe that it is best to start with the conservative ‘safe’ scenario, given the storage of high-cost drugs such as mAbs. The benefit–risk balance needs to be borne in mind: ready-to-use storage versus risk of expiry of the stored bands. It is worth mentioning that literature simulations showed a cost avoidance when using dose rounding of high-cost biological agents or through making DB batch productions (fewer fractions lost).\textsuperscript{13}\textsuperscript{14} Cost avoidance through DB production evidently assumes that expiry on storage is not occurring.

An important criticism is that the dose of intravenous anti-cancer drugs used depends on body surface area (BSA). The correlation between the area under the curve (AUC) of the plasma concentration over time (which is linked to toxicity and efficacy) and BSA is rather poor. This ascertainment could undermine the acceptance of DB built on BSA dosing. Regardless of the fact that some authors have shown no significant difference in precision (AUC versus target AUC in pharmacokinetic models) between using DB ranges and classic BSA dosing, the inaccuracy of BSA remains an important concern.\textsuperscript{13} This cannot be solved with DB.

The real advantage of efficient preparation in oncology is the subcutaneous formulation of mAbs such as rituximab and trastuzumab. These formulations are not included in the above calculations, but today, two out of three preparations of trastuzumab. These formulations are not included in the above calculation, but today, two out of three preparations of trastuzumab. These formulations are not included in the above calculation, but today, two out of three preparations of trastuzumab. These formulations are not included in the above calculation, but today, two out of three preparations of trastuzumab. These formulations are not included in the above calculation, but today, two out of three preparations of trastuzumab. These formulations are not included in the above calculation, but today, two out of three preparations of trastuzumab. These formulations are not included in the above calculation, but today, two out of three preparations of trastuzumab. These formulations are not included in the above calculation, but today, two out of three preparations of trastuzumab. These formulations are not included in the above calculation, but today, two out of three preparations of trastuzumab. These formulations are not included in the above calculation, but today, two out of three preparations of trastuzumab. These formulations are not included in the above calculation, but today, two out of three preparations of trastuzumab.

It is further important to state that the used stability data are strictly linked to the used brand name, infusion volume, final concentration and manufacturer’s data which can all differ between centres.

We make the following future recommendations to other European centres:

► Some shelf lives exceed 3 months, therefore, it is strongly advised from a microbiological aspect that sterility testing should be in place. Our hospital simultaneously uses a validated BacT/Alert 3D microbial detection system (Biomerieux, Durham, USA) to test microbiological stability.

► Before making a new batch of a selected DB strength, an immediate re-evaluation of usage is needed (eg, previous 3 months), correcting for drug use fluctuation over time. This could be carried out with an automated query and protects against expiry.

► We recommend that physicians are clearly informed about which drugs are considered for DB. In our electronic system molecules following LDB are directly converted to pharmacy work through DB enables a more homogeneous occurrence of the CIVA personnel, resulting in better work with the same or fewer personnel. Reduction of the just-in-time preparations in our centre is needed to cover the 5–10% increase in oncological treatments each year.

As a final goal, DB contributes to reduced waiting time in day clinics in addition to other efforts, such as laboratory parameter checks on the day before consultation. If a drug forms part of a chemotherapy doublet or triplet, we believe that the benefit from DB will be the greatest if all drugs of the set are prepared ahead.

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Competing interests None declared.

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