Introduction

Drug expenditure in oncology is constantly increasing. The management of iv chemotherapy preparation is a crucial factor in terms of costs including drug procurement, drug wasting, preparation time, waiting times for patients and other sources of costs (1).

Many chemotherapeutic agents have a narrow therapeutic index so that individualized dosages are calculated considering the patient’s body surface area (BSA), weight or renal clearance. The use of BSA in drug dosing is universally recognized, particularly in oncology, since the 1950s (2).

The need for an accurate dose individualization originates from the low therapeutic index of cytotoxic chemotherapy and from its interpatient variability in therapeutic and toxic effects. In fact, cytotoxic drug clearance can vary up to 4 to 10 times between individuals due to differences in drug metabolism or elimination and other genetic and environmental factors. Furthermore, associations of drugs, nutritional supplements and/or food may alter the metabolism of chemotherapeutic drugs (3).

ABSTRACT

Introduction: Dose banding is an original approach that manages intravenous (IV) chemotherapy preparation by generating on a weekly basis a series of bags containing scaled dosages of the active agent. These predetermined, fixed dosage bags are intended to replace the traditional bags prepared daily that contain fully individualized dosages.

Methods: Three different scenarios were examined: (1) the current method of daily preparation of individualized bags at the hospital pharmacy; (2) the weekly preparation at the hospital pharmacy of non-individualized bags containing discrete, predefined doses covering an adequate range of doses (dose banding); (3) the use of commercial ready-to-use bags based on the same approach of dose banding. The objective of this study was to compare these three different approaches in terms of cost per patient. We considered five cancer drugs (gemcitabine, oxaliplatin, paclitaxel, trastuzumab and 5-fluorouracil) that were suitable for the dose ranging approach. Appropriate dose bands for these five agents were identified. Costs were estimated for each of the three approaches.

Results: A total of 13,490 fully individualized bags were studied, which corresponded to the real bags prepared at our institution for these five agents in 2018. Dose banding was predicted to determine savings ranging from €10,998 (−0.84%) for trastuzumab to €169,429.60 (−8.39%) for paclitaxel.

Conclusion: The introduction of dose banding can determine economic savings along with other advantages, such as improved work conditions, management reorganization and containment of waste. The pharmaceutical industry can hopefully support these experiences by producing ready-to-use bags in predetermined dosages.

Keywords: Antineoplastic agent, Cost analysis, Dose banding, Drug compounding, Economic gain, Time management
Banding in an Italian oncology hospital

The BSA-based dosing strategy depends only on height and weight; therefore, it does not consider the variables that can influence the pharmacokinetic characteristics of drugs (4).

In organizational terms, ensuring that cytotoxic parenteral drugs provide the correct individualized dosage for each patient on a daily basis is a time-consuming process and can cause drug waste (5).

The typical setting in which IV chemotherapeutic agents in hospitals are compounded has evolved markedly over the last 20 years. In Italy, the “Recommendation for the errors prevention in antineoplastic drug therapy” published by the Italian Ministry of Health in 2012, commonly known as “Recommendation 14,” emphasized the importance of in-hospital centralization of chemotherapy compounding and led to the creation of antineoplastic drug units (or UFA—Unità Farmaci Antineoplastici) in hospital pharmacies (6).

In UFAs, hospital pharmacists and technicians work together to provide individualized chemotherapy for each oncologic and/or hematologic patient on a daily basis. Pharmacists’ competences include UFA organization, management and chemotherapy validations. Technicians, on the other hand, are responsible for the final preparation.

To optimize the whole process, in recent times hospital pharmacists are evaluating the option of the “dose banding” strategy as previously described (7).

Adapting the dosing need of each individual patient to the available “banded” dosages can typically be made by rounding the exact dosage or the patient’s body surface (usually at the first decimal) or by using a logarithmic dosing scale.

The “banding dose” approach identifies scaled fixed doses that usually differ by up to 5% of the dose based on BSA, even though some authors have proposed a wider range (e.g., 10%, according to the “National Institute for Health and Care Excellence Key therapeutic topic” [8]). This variation interval is thought to be compatible with normal interpatient pharmacokinetic variability (9).

The dose banding strategy is not new since many hospitals introduced it more than 15 years ago. Studies carried out in the past years indicated no change in efficacy of chemotherapeutic agents with the adoption of standardized doses (7). In addition, further evidence suggests that the use of dose bands not only keeps the efficacy unchanged, it may also improve the toxicity profile (1).

The main substantial difference between the traditional “individualized” method (which is currently in use) and the “proxy” standardized dose of antineoplastic drugs lies in the organizational costs. On the other hand, dose banding has not been uniformly adopted thus far (10-12).

The aim of the present study was to compare the current approach of individualized daily compounding with a dose banding strategy. Our comparative analysis was conducted at the Istituto Oncologico Veneto (IOV). The IOV center, located in Padua, is a public health care institute that carries out prevention, diagnosis and treatment of tumors and at the same time performs clinical research. The IOV is recognized by the Italian Ministry of Health as IRCCS (Scientific Institute for Research, Hospitalisation and Health Care) and Comprehensive Cancer Centre.

Methods

Scenarios under comparison

The current scenario, that is, the current compounding approach used at the IOV (Scenario #1), relies on the daily preparation of individualized bags. The second scenario (Scenario #2) consists in the weekly production at the IOV of predosed bags, that is, the dose banding approach. The third scenario (Scenario #3) involves the purchase of ready-to-use dose banding bags made by a pharmaceutical company or authorized laboratory.

In Scenario #1 (current scenario), the process begins with the medical prescription and the subsequent pharmacist validation of the therapy. The worksheet is then printed and taken to the compounding laboratory where the bags are prepared and checked. Finally, the drug bags are collected by the oncology nurse staff. This scenario leads to a high workload for pharmacists and for the UFA staff.

In the approach of dose banding bags (Scenario #2), the compounding of bags is scheduled on a weekly basis. The bags are prepared, labeled, visually checked and sent to the oncology wards. The expiration date printed on the bag label is shorter than that assigned to the commercial products, so there is a potential risk that some preparations may expire. Predosed bag scheduling should be strictly based on the number of bands weekly prescribed by hospital clinicians.

Scenario #3 provides, after the drug prescription, much fewer phases, namely bag labeling, its packaging, final controls and delivery to the oncology department. This would cut down the compounding time and all the other operations required by compounding. The industry, however, is currently providing only one commercial product that could meet this need.

Comparative analyses

The three scenarios were compared for the following five drugs: gemcitabine, oxaliplatin, paclitaxel, 5-fluorouracil (5-FU) and trastuzumab. These agents were selected firstly because they are largely used and also because they demonstrate chemically stability for at least 1 week after dilution. This choice is supported by specific data published in “Micromedex,” “Stabilis” database and scientific papers (11-16).

Gemcitabine has shown activity in a variety of solid tumors and has been approved for the treatment of non–small cell lung cancer and pancreatic, bladder and breast cancer. Oxaliplatin is used to treat colon or rectal cancer. Paclitaxel is one of the most widely used antineoplastic agents with broad activity in several cancers including ovarian cancer, breast cancer and non–small cell lung cancer. Paclitaxel alone is used as second-line treatment of acquired immunodeficiency syndrome (AIDS)-related Kaposi sarcoma. 5-FU is a pyrimidine analog used as an antineoplastic agent to treat multiple solid tumors including colon, rectal, breast, gastric and pancreatic cancer. Finally, trastuzumab is indicated, as part of a treatment regimen or as a single agent, for the HER2-overexpressing adjuvant breast cancer and metastatic breast cancer and for the treatment of patients with...
HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma in combination with cisplatin and capecitabine or 5-FU. Costs for the current scenario (Scenario #1) and hypothetical Scenarios #2 and #3 refer to 2018.

Dosage bands employed for the five agents

We adopted the dosage bands indicated in a previous report published by our group (17).

Cost analysis

We considered the presence of at least two laboratory technicians to allow for a double check during the compounding phase.

The following direct unit costs were considered:

- Cost of health professionals involved in drugs compounding (nurse and specialized laboratory technician): €21 per hour (gross cost)
- Ex-factory costs of drugs per milligram in 2019 (Tab. I)
- Cost of medical devices required for drugs compounding: €5 per therapy
- Technical/administrative costs (including depreciation and maintenance of premises and equipment) and cost of disposal of cytotoxic waste: €4 per therapy

### TABLE I - Ex-factory costs per milligram of drugs in 2019

| Drug     | Cost per mg (€) |
|----------|-----------------|
| Oxaliplatin | 1.367          |
| Gemcitabine  | 0.067          |
| Paclitaxel    | 2.747          |
| Trastuzumab    | 3.415          |
| 5-Fluorouracil | 0.003         |

All unit costs came from the hospital management control accounting documents and were referred to the hospital pharmacy in 2018.

The total costs for Scenario #1 were calculated by summing up the technicians’ costs, the drug cost per milligram for the assumed annual number of bags, the disposal of cytotoxic waste based on the annual weight of empty bottles, the price of medical devices and the cost of black box prices. In Scenario #2, the costs considered are the same except for the technician costs, considering the reduction of set-up times, also directly affecting the rest of the therapies. In Scenario #3, the incurred costs are mainly related to the price of the medicinal specialty. There are no differences in the cost per milligram of the drugs between the scenarios. The differences between the scenarios are due to the different production processes.

Time analysis

Compounding timing was broken down into the various operational steps according to an activity-based costing (ABC) method (18), that is,

- pharmacy validation and laboratory entry;
- preparation of laboratory materials;
- internal laboratory (laminar flow cabinet) entry and exit;
- packaging.

Time measurements were made on consecutive compounded bags during the daily routine activity. In particular, we measured the compounding times of all the preparations in seven consecutive days each month, for four consecutive months.

For each drug, we calculated the minimum, maximum and average time for each step.

For Scenario #2, we considered the following frame times:

- time of preparation of laboratory materials (average time is 10 minutes for 50 doses);
- preparation time for each dose;
- packaging time (average time is 30 seconds for each dose).

The time intervals of Scenario #2 were derived from the previous time analysis of real-time practice, considering that this is a hypothetical scenario.

Collected times were rounded up or down to the nearest 0.5 seconds.

Results

During 2018, more than 90,000 doses of chemotherapeutic drugs were produced by the UFA located in the IOV, corresponding to about 300 per day. More than 17,000 doses (17,616), equal to 20% of the total doses set up in 2018, were made by one of the five drugs considered in this study. Among these, 13,490 (76.6%) were within the dosage band (Tab. II).

### TABLE II - Feasibility of each drug in several dosage bands

| Drug        | Compounding IOV 2018 (number of doses) | Feasible dose banding (number of doses) | % feasible dose banding |
|-------------|----------------------------------------|----------------------------------------|-------------------------|
| Gemcitabine | 3,752                                   | 3,539                                  | 94                      |
| Paclitaxel  | 6,349                                   | 5,360                                  | 84                      |
| Oxaliplatin | 2,337                                   | 1,295                                  | 55                      |
| Trastuzumab | 2,667                                   | 1,222                                  | 46                      |
| 5-Fluorouracil | 2,511                               | 2,074                                  | 83                      |

IOV = Istituto Oncologico Veneto.

We estimated the mean frame times needed for compounding every dose according to Scenario #1 (Tab. III). Average compounding time for each drug dose ranged from 21 minutes for a single dose of gemcitabine to 40 minutes for a single dose of 5-FU and trastuzumab.

The batch production in Scenario #2 involves a different operational plan. A single batch production could be less convenient than a single production, in terms of total time, but it can significantly reduce the set-up time for each therapy (Tab. IV).
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Each scenario, characterized by different set-up times, has different costs. Table V summarizes costs and differences between the three scenarios. The total savings of Scenario #2 vs. Scenario #1 would amount to €281,058.40; Scenario #3 vs. Scenario #1 would generate total savings of €402,468.40; and €121,410 for Scenario #3 vs. Scenario #2.

Discussion

Currently at IOV center, compounding is based on the daily compounding of individualized bags which is preceded by medical evaluation, blood tests and medical prescription. Scenario #2 (weekly production of dose banding bags at predefined dosages) differs from that currently applied; compounding is planned with fewer constraints and can be organized in time frames with low workload. In this scenario, the preparation time is reduced because the dilution is made in batches and consequently some passages are carried out once (e.g., preparation of medical devices, transfers of vials and bags, and the tray preparation). The process of dilution is carried out sequentially and more likely can reuse production wastes so that technicians’ working time is shorter. At the time of prescription, the bags already prepared and stored in the laboratory are labeled, packaged, checked visually and sent to the ward. In this way, the process is more fluid and efficient but is exposed to risk of expiration of prepared and/or unused bags.

| TABLE III - Mean frame times occurred for one single dose compounding according to Scenario #1 |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Drug            | Pharmacy validation and laboratory entry (min) | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Gemcitabine     | 2.61            | 2.22 | 4.37 | 2.24 | 8.07 | 4.66 | 6.00 | 4.60 | 21.05 |
| Paclitaxel      | 3.68            | 3.14 | 6.08 | 4.18 | 17.03 | 9.8  | 6.91 | 3.68 | 33.70 |
| Oxaliplatin     | 2.64            | 1.12 | 7.60 | 5.49 | 22.40 | 10.30 | 3.45 | 1.58 | 36.09 |
| Trastuzumab     | 4.38            | 3.04 | 6.31 | 3.63 | 21.22 | 9.86 | 8.43 | 1.44 | 40.34 |
| 5-Fluorouracil  | 3.96            | 1.96 | 7.48 | 4.79 | 23.39 | 11.66 | 4.44 | 5.34 | 40.00 |

Table III: Mean frame times occurred for one single dose compounding according to Scenario #1.

| TABLE IV - Batch production in Scenario #2 with different schedules |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Drug            | Batch doses     | Compounding time for lab devices (min) | Total compounding time for batch (min) | Packaging time (min) | Total Time batch preparation (min) | Time/dose preparation (min) |
| Gemcitabine     | 68              | 14              | 136             | 34              | 184             | 2.7             |
| Paclitaxel      | 103             | 21              | 103             | 51.5            | 175.5           | 1.7             |
| Oxaliplatin     | 25              | 5               | 50              | 12.5            | 67.5            | 2.7             |
| Trastuzumab     | 25              | 5               | 100             | 12.5            | 117.5           | 4.7             |
| 5-Fluorouracil  | 40              | 8               | 80              | 20              | 108             | 2.7             |

Table IV: Batch production in Scenario #2 with different schedules.

| TABLE V - Costs and differences between the three scenarios |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Drug            | No of doses     | Total costs Scenario #1 (€) | Total costs Scenario #2 (€) | Total costs Scenario #3 (€) | Savings Scenario #2 vs. #1 (€) | Savings Scenario #3 vs. #1 (€) | Savings Scenario #3 vs. #2 (€) |
| Gemcitabine     | 3,539           | 459,390.54      | 414,055.95      | 382,204.95      | 45,334.59       | 77,185.59       | 31,851           |
| Oxaliplatin     | 1,295           | 317,142.20      | 286,955.75      | 275,300.75      | 30,186.45       | 41,841.45       | 11,655           |
| Paclitaxel      | 5,360           | 2,018,220.90    | 1,897,031.30    | 1,848,791.3     | 121,189.60      | 169,429.60      | 48,240           |
| Trastuzumab     | 1,222           | 1,336,25.75     | 1,306,059.13    | 1,295,061.13    | 30,195.62       | 41,193.62       | 10,998           |
| 5-Fluorouracil  | 2,074           | 80,861.14       | 76,279          | 8,043           | 54,152.14       | 72,818.14       | 18,666           |
| tot             | 281,058.4       | 402,468.4       | 121,410         | 281,058.4       | 402,468.4       | 121,410         |

Table V: Costs and differences between the three scenarios.

The bags reported in this table reflect the needs at our institution for a total of 3 weeks.
The third scenario (purchase of ready-for-use bags) requires only the phases of labeling, packaging and checking after the medical prescription.

With this work, our objective was to investigate the feasibility of introducing dosing bands in an Italian oncology center.

Our method of defining the bands allowed us to identify 10 dosage bands for gemcitabine, 6 for oxaliplatin and trastuzumab, 9 for paclitaxel and 8 for 5-FU, with feasibility values ranging from 46% to 94%.

The possibility to replace an individualized bag with a fixed dose band bag determines a number of advantages. First, the operator’s time is considerably reduced, with a consequent reduction also in the patient’s waiting time at the chair for chemotherapy infusion in day hospital. Second, production in batches allows taking full advantage of the working day and avoiding hours of high workload followed by much less busy hours.

In our analysis, we estimated, through Scenario #3, the use of ready-to-use commercial products. To date, there is only one drug (gemcitabine) commercially available in certain dosage bands. The assessment of the impact of industrial bags needs to be evaluated in much detail especially because many dosage bands would be needed.

Our study has some limitations. First, we studied only five cancer drugs commonly used in daily clinical practice. We selected those drugs because they were largely used and were chemically stable for at least 1 week after dilution. Some of these are also present in different pharmaceutical forms (e.g., trastuzumab subcutaneously) and/or require more complex or special formulations (e.g., 5-FU in syringe pump). For this reason, standardizing the production of IV formulations can guarantee more time for the preparation of technologically more complex pharmaceutical forms.

Another limitation regards the estimation of costs. We decided to evaluate only direct costs related to the use of dosing bands, not considering overhead costs. Also, we did not consider the extent to which medical devices (along with disinfectants and other instruments) are involved in different preparation processes and the consequent amount of production waste.

Our study has collected data from only one center, with its own expertise, history and peculiar management preferences. This can also represent a limitation of the study as the IOV represents a center of oncological excellence. In fact, specialized hospitals are characterized by better management and optimization processes compared to multispecialty hospitals with fewer preparations. Other analyses will be necessary to confirm the hypotheses that emerged from this center, especially with reference to centers of different sizes and with different characteristics.

Conclusion

The process of preparation and production of individualized therapies is a multifactorial system involving all actors in the context of the hospital pharmacy and is influenced by numerous variables. The goal is to operate safely and ensure the quality of the product released, along with working in compliance with regulations and creating as little discomfort as possible for patients.

Our analysis has shown that dose banding can determine a not negligible economic gain.

Other advantages include improved work stress conditions, management reorganization in a “leaner” logic as well as the containment of waste.

The pharmaceutical industry is expected to also support these experiences by manufacturing ready-to-use bags in specific dosages; these could be particularly useful in small and medium-size centers that may not reach the quantity of dosing bands that would make batch production cost-effective.

Our study needs further research to confirm the validity of our data also at other centers. In this way, it may be possible to promote secure batch set-ups through institutions as well.

Disclosures

Conflict of interest: The authors have nothing to disclose. The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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