



Enhancing healthcare economics: the impact of manual dose rounding on T-DM1 costs in breast cancer treatment

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Abstract

Introduction Breast cancer is the second most common cancer worldwide, with HER2-positive disease being an aggressive subtype. Trastuzumab emtansine (T-DM1) has been the gold standard for second-line treatment in HER2-positive metastatic breast cancer since 2012. However, the high cost of cancer treatments presents a significant economic burden. Many oncology drugs, including T-DM1, are dosed on the basis of patient weight, leading to drug wastage due to single-dose vials.

Objective The aim of the study was to determine whether manual dose rounding down can reduce drug wastage and costs.

Methods This retrospective study included patients treated with T-DM1 from January 2015 to December 2022 at the Tampere University Hospital in Finland. Data were collected from chemotherapy and pharmacy software. Drug wastage and cost savings were analyzed.

Results A total of 1797 T-DM1 doses were used over the 8-year study period. The proportion of T-DM1 doses suitable for rounding was on average 67%. Oncologists reduced 31,268 mg of drug waste (74% of total waste) by rounding doses down to the nearest vial size. During the study period, dose rounding resulted in savings of 1,307,659€ (14% of total costs). An additional 609,028€ could have been saved if all possible doses had been rounded down.

Conclusions Manual dose rounding of T-DM1 by oncologists considerably reduced drug wastage and costs. Implementing an automated dose rounding system in the chemotherapy management software would further reduce costs. These findings highlight the importance of innovative healthcare solutions to address the high costs of cancer treatments.

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Introduction

Breast cancer (BC) is the second most common cancer worldwide [1]. In Finland, the annual number of new cases was 4897 in 2022; furthermore, 871 cancer deaths were recorded during the same year [2]. Worldwide in 2022, more than 2 million new BC cases and 665,684 BC deaths were recorded [1]. HER2-positive disease is an aggressive subtype of BC and accounts for 15–20% of all cases. Over the past two decades, diagnostic and treatment advances as well as the development of HER-2 targeted monoclonal antibodies have substantially improved survival outcomes of patients with HER2-positive BC both in the early and metastatic phases [3]. These targeted therapies are now approved for multiple lines in the treatment pathway for HER2-positive metastatic breast cancer (mBC). For first-line treatment, the European Society for Medical Oncology (ESMO) clinical practice guidelines recommend the combination of trastuzumab, pertuzumab, and taxane as the standard of care [4]. For second-line treatment, ado-trastuzumab emtansine

Key Points

Manual dose rounding of T-DM1 saved 1.3 million euros in 8 years in a mid-sized unit in Tampere Finland.

Automated dose rounding could have saved an additional 609,028€.

Effective information management and repetitive reminders increased dose rounding.

This study seeks to evaluate the safety and efficacy of weekly obexelimab administration in reducing IgG4-RD flares.

(T-DM1) has been the gold standard since 2012, based on the EMILIA trial results in which T-DM1 was shown to be superior to capecitabine plus lapatinib as a second-line and further-line treatment in patients with HER2-positive BC [4, 5]. However, the role of T-DM1 as a standard second-line treatment has recently been challenged by the results of the DESTINYBreast03 phase III trial, which compared trastuzumab deruxtecan (T-DXd) with T-DM1 in patients previously treated with a combination of taxane and trastuzumab [6]. T-DXd demonstrated improved overall survival (OS, HR 0.55; 95% CI 0.36–0.86; $p = 0.007$) compared with T-DM1. In addition, T-DM1 has also been used as an adjuvant therapy in patients with early HER2-positive BC who had residual invasive disease after neoadjuvant chemotherapy for a few years. This has been shown to improve overall survival [7].

The growing elderly population has gradually increased the number of new cancer cases, since the most important risk factor for cancer is age, thus increasing the economic cost of cancer treatments all over the world [8]. Escalating cancer drug prices present global challenges to treatment access and cancer outcomes [9]. In terms of global cancer costs, BC is the third most expensive cancer type [8]. Costs are gradually increasing and in the USA alone, and it has been estimated that 3.2€ (3.6 USD)–6.9€ (7.6 USD) trillion will be spent on breast cancer by the year 2035 [10, 11]. A recent study by Mahtani et al. estimated that a major portion of BC-related costs were associated with these HER2-targeted treatments. The 3-year cumulative all-cause and BC-related total costs were 674,768€ (769,573 USD) and 547,527€ (624,455 USD), respectively [11, 12]. According to these findings, treatment of HER2-positive mBC seems to be a substantial economic burden.

Many oncology drugs are dosed either on the basis of patient's weight or body surface area. When using these dosing methods, additional drug quantities are often needed due to the available vial sizes, requiring one full vial plus

a portion of another. Since many of these drugs come in single-dose vials (SDVs), the leftover portion of the vial is discarded, leading to significant drug waste and increasing the cost of healthcare [13].

According to the recommendation of the Hematology/Oncology Pharmacy Association (HOPA), when possible, the dose should be rounded down to the nearest whole vial considering that the lowering of the dose does not exceed 10% of the entire dose [14]. Numerous reports highlight the potential and actual wastage minimization and cost savings achieved through automated dose-rounding of intravenous anticancer agents [15–17]. These studies indicate that biologic therapy offers greater potential for cost savings due to their higher costs and longer treatment durations compared with conventional chemotherapy agents. However, these studies lacked data on the financial impact of manually rounding off the dose of cancer medication by the oncologist.

Introducing the T-DM1 into clinical use at Tampere University Hospital (TaUH) in 2015, oncologists were recommended to round the dose to the nearest whole vial size when it was clinically possible. The TaUH's dose rounding recommendation was made prior to the HOPA's recommendation and without a certain percentage limit. The aim of this study was to retrospectively evaluate implementation of the manual T-DM1 dose rounding recommendation and its financial consequences at TaUH, the second largest university hospital in Finland.

Materials and methods

This retrospective study was conducted at the Department of Oncology of TaUH, Finland. We included the records of patients treated between January 2015 and December 2022. The study included all adult cancer patients (older than 18 years of age) who received T-DM1. The details were recorded on the basis of the information obtained from the chemotherapy management software (Kemokur™, CGI Finland Oy, Helsinki, Finland) and hospital pharmacy software (Marela, CGI Finland Oy, Helsinki, Finland). The information recorded included height, weight, date of dosing, T-DM1 dose formulation (mg/kg), unrounded dose, and rounded dose. The recommended dose of T-DM1 of 3.6 mg/kg was given as an intravenous infusion every 3 weeks. The recommended dose reduction schedule for adverse reactions was for a first dose reduction of 3 mg/kg and a second dose reduction of 2.4 mg/kg. T-DM1 is available in two vial sizes: 100 mg and 160 mg. Information about the size and prices of the T-DM1 vials was recorded in the chemotherapy order templates of Kemokur™ software and hospital pharmacy software.

Our analysis of drug wastage included the following scenarios: (1) calculation of the unused

drug amount by subtracting the original dose calculated by Kemokur™ from the total amount of the drug in the vial in mg and (2) calculation of wasted drug and drug costs in real-life situations by using prescribed doses that were not rounded down and prescribed doses that were rounded down.

The study was approved by the local institutional review board at TaUH (study no. R23550). Ethics Committee evaluation and written informed consent are not required in single-institution register-based studies in Finland.

Results

A total of 1797 T-DM1 doses were identified and analyzed from the whole 8-year study period. The number of patients, infusions, milligrams of drugs available and administered, and estimates of overall waste are displayed annually, as presented in Table 1.

The proportion of doses suitable for dose rounding was high among T-DM1 administrations (average 67%, range 54–85%). The proportion of doses rounded down by clinical oncologists from the total amount of doses suitable for dose rounding varied annually between 29% and 71% (Table 1). There was a decrease in rounded doses during the years 2018 and 2019. In 2019 oncologists were reminded of the

Table 1 Patient and T-DM1 demographics and proportions of dose rounding

Year	2015	2016	2017	2018	2019	2020	2021	2022
Number of patients	19	21	23	24	32	39	30	35
Number of administrations	160	203	201	192	254	266	248	273
Mean number of administrations per patient	8.4	9.7	8.7	8.0	7.9	6.8	8.3	7.8
Mean amount of an administration, mg	213	244	247	247	241	237	235	247
Maximum amount of an administration, mg	360	360	400	380	356	470	445	360
Minimum amount of administration, mg	150	130	145	190	130	160	155	135
The proportion of all doses that could be rounded, %	85	71	79	64	54	58	63	62
The proportion of doses rounded by clinical oncologists out of all doses that could be rounded, %	83	78	70	46	58	65	78	69
The proportion of rounded doses in the same patients, %	98	97	99	98	98	97	98	99

Fig. 1 Proportion of doses rounded by doctors out of all doses suitable for rounding along with extra costs of wasted vials, presented annually

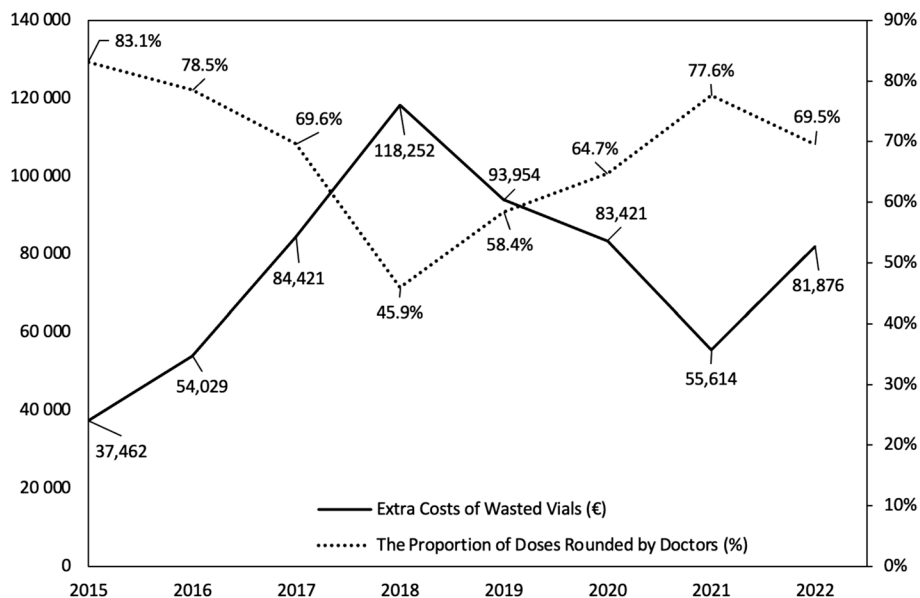


Table 2 T-DM1 waste and costs during the study period

Year	2015	2016	2017	2018	2019	2020	2021	2022
Price of one vial* (100 mg), €	1629	1688	1688	1620	1620	1545	1545	1545
Actual costs of drugs administered, €	698,930	941,014	953,874	943,201	1,163,235	1,102,770	1,008,876	1,158,346
Actual savings by dose rounding, €	184,052	190,790	185,725	90,714	129,591	152,938	186,924	186,924
Potential vial savings, n**	23	32	50	73	58	54	36	53
Potential cost savings, €***	37,462	54,029	84,421	118,252	93,954	83,421	55,614	81,876

*The actual cost of a vial for the current year

**Number of 100 mg vials that could also have been saved if the portion had been rounded down

***Cost savings that were not realized when all doses were not rounded down

dose rounding, and after that the number of rounded doses increased markedly, as seen in Fig. 1.

During the study period, the number of patients and T-DM1 administrations increased. However, the mean number of administrations per patient and the mean number of administrations remained at the same level (Tables 1, 2). If the first drug dose was rounded, the subsequent doses were usually rounded even up to 99% (Table 1). All manual rounding downs of the T-DM1 were within 10% of the prescribed dose specified by the oncologists.

The rounding of the T-DM1 doses by oncologists brought considerable cost savings during the study period (1,307,659€; 14% of total costs). The total costs of the T-DM1 were 7,970,246€. In addition, 609,028€ savings would have been obtained if all roundable doses had been rounded. Without dose rounding, 21% of T-DM1 costs would have consisted of avoidable drug waste costs. Across the cohort, a total of 446,304 mg of T-DM1 was administered to patients. Oncologists reduced 31,268 mg of drug waste (74% of total waste) by rounding down doses to the nearest vial size. From 2015 to 2022, the cost of T-DM1 nearly doubled. During the same period of time, the number of possible saved vials increased from 23 to 53 (Table 2).

Discussion

The implementation of manual rounding down doses by clinical oncologists has yielded a substantial reduction in T-DM1 cost. We observed cost savings of 1,307,659€ (14%) during the 8-year study period. In addition, 609,028€ (7%) cost savings would have been obtained, if automated dose rounding rules would have been implemented in the chemotherapy management software. TaUH is responsible for treating roughly 10% of all patients with breast cancer in Finland [2]. Therefore, we can assume that over 19 million euros in savings could have been realized in Finland with automated dose rounding during the 8-year study period,

i.e., more than 2 million euros per year. In a recent study, the Mayo Clinic implemented automated dose rounding rules in their electronic system, which included more than 90 cancer drugs. By rounding down doses to a whole vial size, savings of 39.75 million USD (35.39 million euros) were achieved in 3 years. These results highlight the significant impact of automated dose rounding on healthcare economics and underscore the expense of neglecting electronic healthcare system development.

Clinical oncologists manually rounded down a large proportion of T-DM1 doses, indeed on average, 68% out of all doses that could have been rounded. This is in accordance with or somewhat better than healthcare providers' adherence to breast cancer clinical guidelines, which ranged from 54% to 69% for the overall treatment process in Europe [18]. According to our results during the first couple of years, oncologists remembered and applied the instructions for rounding the dose quite well, but subsequently the proportion of rounded doses decreased. A reminder of the instructions increased rounding of doses. The results show that we should not solely rely on the clinicians' memory, and the practice should be included as part of the doctors' training program and regular reminders should be issued.

The clinic's recommendation was to round down the T-DM1 dose if this was clinically possible without percentage limits. The manual rounding of the T-DM1 was within 10% of the prescribed dose by oncologists, which is in line with HOPA recommendations [14]. HOPA recommendations are based on the researched knowledge and expert opinions with a consensus that if the rounding down of the dose is within the recommendation limit of 10%, it does not effect the patient outcome. As the clinicians cooperated with the clinic's recommendation, it also showed their trust in the guideline.

It was possible in the present study to round down a surprisingly large proportion of T-DM1 doses, on average 67% of all drug doses, while only an average of 36% of T-DM1 doses were rounded in the study by Shah et al. [17]. According to our study, the key element to a successful practice was the rounding of the first dose: If the first drug dose was

rounded down, the subsequent doses were usually rounded. This is explained by the functionality of the Kemokur™ software. This software makes it possible to copy the previously prescribed dose into the next cycle, which is easier to do in the software than to prescribe the medicine again from the beginning. This is an excellent example of how the functionality of the software guides the doctors' actions.

According to a study by Leung et al. in 2017, drug waste accounts for 4–18% of all cancer drugs used in the USA [19]. In our study if drug rounding had not been used, 21% of the T-DM1's costs would have consisted of medical waste. This is in line with a study by Truong et al. in 2017, which determined that drug waste increases cancer treatment costs by an average of 21.8% [20]. Leung et al. also analyzed the pharmaceutical waste costs of 20 anticancer drugs that are dosed according to the patient's body surface area or weight and packaged in single-dose vials, which altogether accounts for 93% of the sales of such drugs. According to their study, in 2016 the cost of leftover and discarded drugs from these cancer drugs was 1.8 billion USD (1.6 billion euros). The quantity and cost of the remaining drugs varied according to the available vial sizes [19].

As cancer costs increase worldwide, the need for simple methods to reduce drug waste becomes even more significant. In Europe, cancer drug costs have more than doubled between 2005 and 2014, from 8 billion to 19.8 billion USD (1.76 billion euros). In Finland, the corresponding cancer drug costs have increased annually by about 10% during the same time period [21].

The potentially significant proportion of wasted cancer drugs in the total cost of cancer treatment can be considered a hidden cost, as most oncologists are unlikely to be aware of the amount of drugs wasted when prescribing a specific drug and dose for a given patient [22]. In this study the success of rounding down was based on well-designed information management: information about vial sizes and prices was included in the chemotherapy order templates for oncologists to utilize when they prescribe expensive drugs, such as T-DM1, to reduce waste and costs.

As highlighted by the American Society of Clinical Oncology (ASCO)'s Climate Change Task Force, modern healthcare is a major polluter, responsible for more than 5% of all global emissions [23]. To integrate sustainability, we can start by minimizing drug wastage. At the present, the quickest way to reduce drug wastage is to adopt a dose rounding process. Dose sharing or multiple dose vials is another strategy. A study by Leung et al. identified that dose sharing of 14 chemotherapy drugs across three hospitals prevented about 15% of cancer drug wastage [19]. Furthermore, additional vial sizes have been proposed to pharmaceutical companies to reduce drug residue [13].

The strength of this study is the real-world setting and data, which show us a significant need for adjustment in

our everyday practice. Therefore, even the retrospective approach cannot be considered as a weakness. Furthermore, the fact that the clinicians were not aware that this type of study would be done in the future enhances the real-world setting. In addition, the data were collected comprehensively. Weaknesses of the current study include a relatively small sample size and a single institution study.

Conclusions

According to our data, manually rounding the doses of just one drug, T-DM1, in a mid-sized oncology unit led to approximately 1.3 million euro in savings over an 8-year period. By a simple automated drug dose calculation system, instead of relying on the clinicians' memory and manual modification of dosage, the savings of cancer treatment costs could be even more substantial.

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Declarations

Author contributions Luotonen has done the original data analysis and is responsible for the original manuscript draft. Other authors have been part of the investigative process, interpreting the data analysis, have donated their expertise, and have also been part of the manuscript writing process. Vuorinen is the corresponding author. All authors have read and approved the final version of the manuscript.

Data availability The datasets generated and analyzed during the current study are not publicly available due to the risk of compromising privacy.

Code availability Not applicable.

Ethics approval and consent to participate Ethics Committee evaluation and written informed consent are not required in single-institution register-based studies in Finland.

Consent for publication A consent is not required in a register-based study as it does not influence the care of the patients and as the patients cannot be identified on the basis of the research report.

Competing interests Tiainen L. has received consulting or advisory honoraria from Bristol-Myers Squibb, Daiichi-Sankyo, MSD, Novartis, Pfizer, and Roche. All remaining authors, Luotonen, Vuorinen, Kellokumpu-Lehtinen, and Bärlund, have no competing interests to declare that are relevant to the content of this article.

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