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Non-drug related costs of treatment with pertuzumab and trastuzumab in HER2-positive breast cancer patients in Poland

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ABSTRACT

Introduction. HER2-positive breast cancer represents 10–20% of all breast tumors. This study aimed to create a model-based cost-minimization analysis that compared non-drug related costs of different therapies used in the treatment of HER2-positive breast cancer in Poland: pertuzumab SC plus trastuzumab SC (Pert/TrasSC) vs. pertuzumab IV plus trastuzumab IV (PertIV + TrasIV) vs. pertuzumab IV plus trastuzumab SC (PertIV + TrasSC).

Material and methods. The cost-minimization analysis was based on the results of a questionnaire addressed to leading oncology centers in Poland. The model was broken down into three categories of cost savings: reduced labor costs of nurses, pharmacists and non-drug related consumables, and from two categories of treatment time reduction: occupation of infusion chair and duration of hospital stay. Data on resources used and costs were collected in the first half of 2022.

Results. Data were obtained from four oncology centers. The savings generated per patient from healthcare personnel's work and from non-drug consumables for the Pert/TrasSC arm were 178 PLN compared to PertIV + TrasIV and 168 PLN compared to PertIV + TrasSC. Full adaptation of Pert/TrasSC was estimated to result in average 8-fold higher savings in healthcare personnel workload per patient and in a treatment capacity increase of 241 patients.

Conclusions. Our model shows that Pert/TrasSC treatment is associated with significantly lower labor costs for nurses and pharmacists and lower costs of non-drug consumables compared to the other treatment options. Moreover, it reduced patients' chair time due to shorter administration/observation time and released capacity in chemotherapy infusion sites.

Keywords: non-drug costs, HER2-positive breast cancer, pertuzumab, trastuzumab, subcutaneous, PH FDC SC, pharmacoeconomics

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Introduction

Breast cancer (BC) is the most common malignant neoplasm in women, both in Poland (25.3%) and in the European Union (28.7%) [1]. According to the data from the National Cancer Register, in 2017 over 19.6 thousand

people were newly diagnosed with BC in Poland, while in 2008 there were almost 4 thousand fewer new cases, which illustrates the constant growth of the population suffering from this disease [2]. The incidence rate of BC (standardized by age) was 119.1 per 100,000 people in Poland in 2020, and the European average (EU-27) was 142.8 [3].

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In Europe, breast cancer (16.5%) is the most common cause of death in women with neoplastic diseases, while in Poland it is the second (16.4%) most common cause of death after lung cancer [1]. The standardized mortality rate in Poland in 2020 was estimated at 41.8 per 100 000, which was one of the worst results in Europe [3]. According to the Eurostat data, this cancer was responsible for more than a quarter (26.5%) of all deaths from curable diseases in women [4].

A properly selected path of diagnosis and treatment for each patient with BC has a significant impact on their prognosis, survival, and quality of life. Therefore, comprehensive care for BC patients should take place in centers with a team of experienced specialists in various fields, including oncological surgeons experienced in breast reconstructive surgery, clinical oncologists, radiotherapists and radiologists, psycho-oncologists, and physiotherapists [3]. In Poland, only 9 centers were accredited to meet the Breast Cancer Unit (BCU) requirements, and 10 hospitals provide oncological care in the KON-Piers system (1 of them has BCU status) [3].

HER2-positive BC represents 10% to 20% of all breast tumors and has more aggressive behavior [5]. These tumors grow faster and metastasize more frequently beyond the breast compared to HER2-negative breast cancers. HER2-positive BC can be treated with anti-HER2 targeted agents that stop uncontrolled tumor growth [1].

In recent years, significant progress has been made in the development of diagnostic and therapeutic methods in BC management [3]. With a variety of HER2-targeted therapies approved and implemented in clinical practice, the historically adverse prognosis of HER2-positive breast cancer has improved significantly. Dual HER2 blockade with trastuzumab and pertuzumab combined with cytotoxic agents is the treatment of choice in both the neoadjuvant and metastatic setting [6, 7].

On June 29, 2020, the Food and Drug Administration (FDA) approved a new method of treatment for patients with HER2-positive BC with pertuzumab, trastuzumab, and hyaluronidase-zzxf combined in a single formulation (PH FDC SC) [8]. This treatment provides a *subcutaneous* (SC) route of administration for pertuzumab and trastuzumab over 5 to 8 minutes, every 3 weeks, offering breast cancer patients an alternative to *intravenous* (IV) pertuzumab and intravenous trastuzumab [9]. Patients treated with PH FDC SC must have HER2-positive tumor status, defined as a score of 3+ by immunohistochemistry and/or a ratio of ≥ 2.0 by in situ hybridization, assessed by a validated test [10]. The FDA approval was based on the results of a non-inferiority phase III study (FeDeriCa) that demonstrated equivalent efficacy and

safety compared to an intravenous combination of trastuzumab and pertuzumab [11, 12].

The presented analysis aimed to estimate non-drug related cost differences between treatment with pertuzumab and trastuzumab in HER2-positive breast cancer in Poland.

Material and methods

A model-based cost-minimization analysis was performed to compare non-drug-related costs of three different therapies: pertuzumab SC plus trastuzumab SC (Pert/TrasSC; PH FDC SC), pertuzumab IV plus trastuzumab IV (PertIV + TrasIV) and pertuzumab IV plus trastuzumab SC (PertIV + TrasSC) used in the treatment of HER2-positive BC in Poland. Cost-minimization analysis was based on the results of a questionnaire sent to eight leading oncology centers located in Warsaw, Cracow (two hospitals), Szczecin, Gdansk, Lodz, Bydgoszcz, and Kielce. Data were obtained from four centers (Warsaw, two from Cracow, Szczecin). The remaining centers refused to participate in the questionnaire due to lack of time or difficulty in collecting data for the questionnaire. The answers were based on the data of patients with HER2-positive BC treated in selected centers in 2021. Data on resources used and costs were collected in the first half of 2022.

The survey consisted of questions about:

- number of patients treated in oncology centers (treated with each of the aforementioned pertuzumab plus trastuzumab regimens);
- organization of work in the chemotherapy room (the number of working doctors/nurses and working hours/days per day/week);
- parameters related to chemotherapy sessions: chair time (time between entry and exit of the patient using the infusion chair), observation time (time of hospital stay of the patient after the end of chemotherapy);
- information on working hours of healthcare personnel (HCP) involved in preparation/administration of drugs — active HCP: mean time spent on preparation of drugs by pharmacists, mean time spent on a patient by medical staff during chemotherapy session/after the end of chemotherapy session;
- the amount and total costs of medical supplies (consumables) used in each therapy,
- average hourly working rate of nurses and pharmacists.

The survey results worked as the input data for the model estimating the non-drug cost difference between Pert/TrasSC, PertIV + TrasIV, and PertIV + TrasSC. The model was broken down into

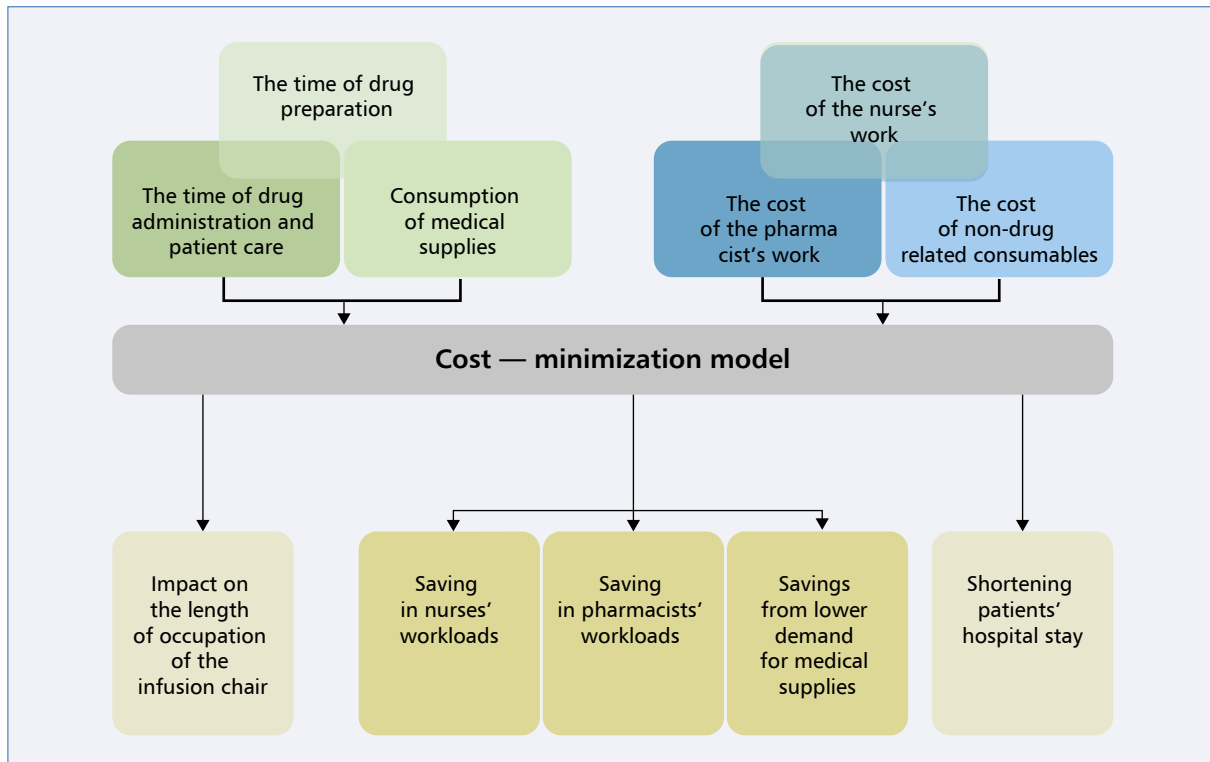


Figure 1. Model overview

three categories of cost savings generated by decreasing nurses'/pharmacists' workloads and demand for non-drug related consumables, and two categories of time savings: shorter occupation of the infusion chair and shorter duration of the hospital stay, which is displayed in Figure 1.

Results

Results of the questionnaire

Of all participating oncology centers, only one hospital treated patients with HER2-positive BC using all three regimens, including Pert/TrasSC therapy. Therefore, in the model, the data from this facility were used to calculate cost differences in other hospital centers. In total, 240 patients were treated with PertIV + TrasIV, 200 patients with PertIV + TrasSC, and 6 patients with Pert/TrasSC, which is summarized in Table 1.

Apart from one facility that worked 6 days a week, 12 hours a day, the others worked from Monday to Friday, 8 or 11 hours, which is presented in Table 2.

On average, 2 to 4 doctors and 2 to 5 nurses worked during a shift, as displayed in Table 3.

In Pert/TrasSC, the time between the patient's entry to and exit from the infusion chair was more than twice shorter than in the PertIV + TrasSC regimen and even 4-fold shorter compared to full IV administration. The time of hospital stay of the patient after the end of chemotherapy was much shorter in the full SC regimen compared to the other treatment regimens, as summarized in Table 4.

The average time spent on Pert/TrasSC preparation by the pharmacist was estimated at 2 minutes and was much shorter compared to other treatment options: 27 minutes with PertIV + TrasIV and 20 minutes with PertIV + TrasSC, which is presented in Table 5. The average time spent by nurses during a chemotherapy session with one patient was: 35 minutes with PertIV + TrasIV, 30 minutes with PertIV + TrasSC, and 25 minutes with Pert/TrasSC. There was also a large difference in the average time nurses spent on a patient after a chemotherapy session between Pert/TrasSC and the other treatments — 15 minutes vs. 120 minutes, which is displayed in Table 6. The time reduction achieved by Pert/TrasSC in active HCP time was driven by fewer tasks being performed in the drug preparation area and less time spent by HCP observing patients after chemotherapy sessions.

Table 1. Number of treated patients in participating oncology centers

	PertIV + TrasIV	PertIV + TrasSC	Pert/TrasSC	Summary
Oncology center 1	10	129	0	139
Oncology center 2	122	54	6	182
Oncology center 3	40	15	0	55
Oncology center 4	68	2	0	70
Summary	240	200	6	446

Pert/TrasSC — pertuzumab subcutaneous plus trastuzumab *subcutaneous*; PertIV — pertuzumab *intravenous*; TrasIV — trastuzumab *intravenous*; TrasSC — trastuzumab *subcutaneous*

Table 2. Working hours per week in the chemotherapy room

	Working days per week	Working hours per day	Working hours per week
Oncology center 1	5	11	55
Oncology center 2	5	11	55
Oncology center 3	5	8	40
Oncology center 4	6	12	72
Average	5.25	10.5	55.5

Table 3. Medical staff in the chemotherapy room

	Average number of doctors	Average number of nurses	Summary
Oncology center 1	3.0	5.0	8.0
Oncology center 2	2.0	2.0	4.0
Oncology center 3	2.0	3.0	5.0
Oncology center 4	4.0	4.5	8.5
Average	2.8	3.6	6.4

Table 4. Average chair time and observation time patients

	PertIV + TrasIV		PertIV + TrasSC		Pert/TrasSC	
	Chair time [min.]	Observational time [min.]	Chair time [min.]	Observational time [min.]	Chair time [min.]	Observational time [min.]
Oncology center 1	90	120	60	120	–	–
Oncology center 2	80	120	50	120	25	15
Oncology center 3	120	120	60	120	–	–
Oncology center 4	120	120	60	120	–	–
Average	102.5	120	57.5	120	25	15

Pert/TrasSC — pertuzumab subcutaneous plus trastuzumab *subcutaneous*; PertIV — pertuzumab *intravenous*; TrasIV — trastuzumab *intravenous*; TrasSC — trastuzumab *subcutaneous*

Due to incomplete data on the average time physicians spent on a patient during a chemotherapy session, this parameter was not analyzed. Only two facilities reported the time that physicians dedicate to patients while administering chemotherapy, and the other two, including Oncology center 2, which was the only facility that treated patients with the Pert/TrasSC regimen,

indicated that they were unable to estimate it. Therefore, we assumed that labor costs of the physicians were the same in each treatment regimen, and they did not influence our analysis.

The average cost of non-drug consumables used in PertIV + TrasIV and PertIV + TrasSC was 51.79 PLN or 59.67 PLN (depending on infusion device) per

Table 5. Average time spent on drug preparation by pharmacist (in minutes)

	PertIV + TrasIV	PertIV + TrasSC	Pert/TrasSC
Oncology center 2	20	20	2
Oncology center 3	30	20	0
Oncology center 4	30	20	0
Average	26.7	20	2

Pert/TrasSC — pertuzumab subcutaneous plus trastuzumab *subcutaneous*; PertIV — pertuzumab *intravenous*; TrasIV — trastuzumab *intravenous*; TrasSC — trastuzumab *subcutaneous*

Table 6. Average time spent on a patient by nursing staff during/after chemotherapy (chemo) session (in minutes)

	PertIV + TrasIV		PertIV + TrasSC		Pert/TrasSC	
	During chemo	After chemo	During chemo	After chemo	During chemo	After chemo
Oncology center 1	20	120	15	120	–	–
Oncology center 2	40	120	35	120	25	15
Oncology center 3	40	120	35	120	–	–
Oncology center 4	40	120	35	120	–	–
Average	35	120	30	120	25	15

Pert/TrasSC — pertuzumab subcutaneous plus trastuzumab *subcutaneous*; PertIV — pertuzumab *intravenous*; TrasIV — trastuzumab *intravenous*; TrasSC — trastuzumab *subcutaneous*

Table 7. Average costs of non-drug consumables used in each therapy per patient

Medical supplies	PertIV + TrasIV	PertIV + TrasSC	Pert/TrasSC
<i>Intravenous</i> cannula or Vascuport needle	2.27 PLN or 9.99 PLN	2.27 PLN or 9.99 PLN	–
Needle	–	–	0.03 PLN
Opaque infusion giving set	37.37 PLN	37.37 PLN	–
Syringe	0.16 PLN (or 0.32 PLN if Vascuport)	0.16 PLN (or 0.32 PLN if Vascuport)	0.16 PLN
Sodium chloride	1.67 PLN	1.67 PLN	–
Luer Lock plug	0.30 PLN	0.30 PLN	–
Seal for infusion bag	2.27 PLN	2.27 PLN	–
Sterile swabs	0.10 PLN	0.10 PLN	0.10 PLN
Sterile hand gloves	1.60 PLN	1.60 PLN	–
Non-sterile hand gloves	0.90 PLN	0.90 PLN	0.30 PLN
Sterile bandage for puncture	2.07 PLN	2.07 PLN	0.30 PLN
Securing tape	2.93 PLN	2.93 PLN	0.00 PLN
Fabric plasters	0.15 PLN	0.15 PLN	0.15 PLN
Summary	51.79 PLN (<i>intravenous</i> cannula) or 59.67 PLN (Vascuport)	51.79 PLN (<i>intravenous</i> cannula) or 59.67 PLN (Vascuport)	1.04 PLN

Pert/TrasSC — pertuzumab subcutaneous plus trastuzumab *subcutaneous*; PertIV — pertuzumab *intravenous*; TrasIV — trastuzumab *intravenous*; TrasSC — trastuzumab *subcutaneous*

patient, whereas in Pert/TrasSC it was only 1.04 PLN, which is presented in Table 7. These savings resulted mainly from the lack of costs of the opaque infusion set and intravenous line in Pert/TrasSC treatment.

Based on results from the questionnaire the average hourly working rate of a nurse is 50.00 PLN and of a pharmacist 54.00 PLN. These data were used as input data to estimate the non-drug cost difference between

Pert/TrasSC and IV administration generated from nurses' and pharmacists' work.

Results of the cost-minimization model

In the cost-minimization model, the following assumptions were made:

- for each oncology center, the same number of patients was assumed for each method of treatment;
- the time of Pert/TrasSC administration was adopted for all centers on the basis of the data from the only facility (participating in the questionnaire) treating patients with this regimen today;
- savings in nursing time were the most important component of hospital costs;
- according to the information provided by the cancer centers, the model assumed that the drugs were prepared by pharmacists.

Simulation using input data from questionnaires showed that depending on the oncology center, patients using Pert/TrasSC treatment would occupy from 0.4 to almost 1.4 infusion sites per week, which was a large reduction compared to other treatments — 1.0 to 4.4 (Fig. 2).

Taking this into account, we can assume that if we replaced existing treatment regimens with trastuzumab and pertuzumab by Pert/TrasSC, an average of 241 additional patients could be treated in all participating oncology centers (Tab. 8).

The model showed that if all patients in all participating oncology centers were treated with Pert/TrasSC, the hospitals would save 8-fold more hours (3 345 vs. 26 760 hours) compared to the other regimens (Tab. 9).

The cost minimization model showed that the average savings (per patient) generated by the reduced workload of nurses using Pert/TrasSC treatment amounted to nearly 96 PLN compared to PertIV + TrasIV and 92 PLN for PertIV + TrasSC. The average savings (per patient) generated by the reduced workload of pharmacists for Pert/TrasSC were 22 PLN and 16 PLN compared to PertIV + TrasIV and PertIV + TrasSC, respectively (Tab. 10). The model showed that the costs of non-drug consumables for Pert/TrasSC treatment were significantly lower than in the case of the other existing treatment regimens – the savings (per patient) were 60 PLN.

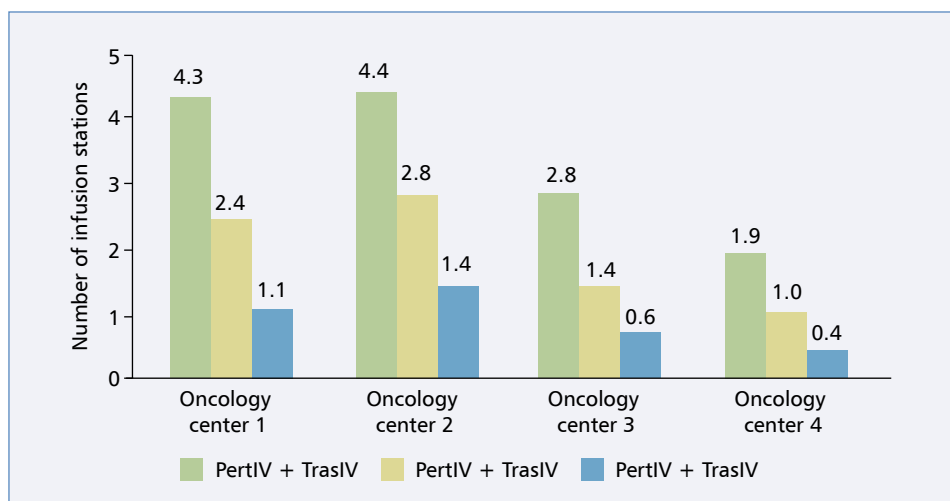


Figure 2. Number of infusion stations occupied by patients for all treatment regimens based on the model assumptions

Table 8. Number of additional patients who could receive treatment in the studied facilities if the existing regimens were replaced with *pertuzumab subcutaneous plus trastuzumab subcutaneous* (Pert/TrasSC)

	PertIV + TrasIV	PertIV + TrasSC	Summary
Oncology center 1	26	181	207
Oncology center 2	268	54	322
Oncology center 3	152	21	173
Oncology center 4	258	3	261
Average			241

PertIV — pertuzumab *intravenous*; TrasIV — trastuzumab *intravenous*; TrasSC — trastuzumab *subcutaneous*

Table 9. Time spent in the hospital by patients (post-chemotherapy observation time in hours)

	PertIV + TrasIV	PertIV + TrasSC	Pert/TrasSC
Oncology center 1	8 340	8 340	1 043
Oncology center 2	10 920	10 920	1 365
Oncology center 3	3 300	3 300	413
Oncology center 4	4 200	4 200	525
Summary	26 760	26 760	3 345

Pert/TrasSC — pertuzumab subcutaneous plus trastuzumab *subcutaneous*; PertIV — pertuzumab *intravenous*; TrasIV — trastuzumab *intravenous*; TrasSC — trastuzumab *subcutaneous*

Table 10. Labor cost of nurses/pharmacists work, and non-drug consumables per patient for each treatment option

Total cost per patient of:	PertIV + TrasIV	PertIV + TrasSC	Pert/TrasSC	Savings:	
				Pert/TrasSC vs. PertIV + TrasIV	Pert/TrasSC vs. PertIV + TrasSC
Nurse labor cost	129.17 PLN	125.00 PLN	33.33 PLN	95.83 PLN	91.67 PLN
pharmacist's labor cost	24.00 PLN	18.00 PLN	1.80 PLN	22.20 PLN	16.20 PLN
medical supplies	59.67 PLN	59.67 PLN	1.04 PLN	58.63 PLN	58.63 PLN
Summary	212.84 PLN	202.67 PLN	36.17 PLN	176.66 PLN	166.50 PLN

Pert/TrasSC — pertuzumab subcutaneous plus trastuzumab *subcutaneous*; PertIV — pertuzumab *intravenous*; TrasIV — trastuzumab *intravenous*; TrasSC — trastuzumab *subcutaneous*

The largest savings for Pert/TrasSC came from the reduced labor costs of nurses: 54–55% of total savings compared to other regimens. The model showed that Pert/TrasSC treatment was associated with significantly lower labor costs for nurses and pharmacists, and lower costs of non-drug consumables, generating total savings of nearly 177 PLN compared to PertIV + TrasIV and 167 PLN compared to PertIV + TrasSC (Tab. 10).

Discussion

Clinical Practice Guidelines in Oncology issued by the National Comprehensive Cancer Network (NCCN) state that pertuzumab, trastuzumab, and hyaluronidase-zzxf injection for subcutaneous use may be substituted in patients who receive IV pertuzumab plus trastuzumab as part of systemic therapy for HER2-positive BC [13]. This improved formulation of the cornerstone therapy for HER2-positive BC can have positive effects on patients and the healthcare system. The presented cost-minimization analysis aimed to estimate potential cost differences between Pert/TrasSC, PertIV + TrasIV, and PertIV + TrasSC. The model was based on a questionnaire sent to eight leading oncology centers; however, only 50% of the hospitals answered the survey. Total savings generated from reduced workloads of nurses/pharmacists and reduced costs of non-drug consumables in the treatment of HER2-positive BC in

Poland using trastuzumab and pertuzumab regimens were calculated. This analysis also studied the impact of different therapies on occupation of infusion sites during chemotherapy sessions and duration of patient hospital stay.

The model demonstrated that Pert/TrasSC treatment was associated with savings in each analyzed cost category. These savings were largely driven by shorter patient chair time, less active HCP time, and reduced non-drug consumable costs. Our findings were consistent with the literature. There are several studies demonstrating that switching from intravenous pertuzumab and trastuzumab to Pert/TrasSC resulted in reduced non-drug costs for healthcare providers mainly through time savings and improved patient satisfaction [14–17]. Notably, the feasibility of the Pert/TrasSC administration in patients' homes was also reported, which has the potential to further optimize HCP workload and patients' quality of life [18, 19].

Reduction in nurses' workload not only brought savings for the hospital budget but was also associated with a positive influence on organizational and systemic aspects. According to the OECD report Health at a Glance 2021 [20], Poland, with a small number of professionally active nurses (an average of 5.1 per 1 000 inhabitants) is in the penultimate place in the EU, with Lithuania in the last place. By comparison, countries such as Switzerland and Norway have an average of 18 nurses per 1000 inhabitants. Due to drastic shortages of nursing staff that

hospitals must deal with, the difference in active HCP time of more than 100 minutes per treatment session is a very important factor for hospitals supporting the use of Pert/TrasSC. Our simulation showed that if we replaced the other treatment regimens with Pert/TrasSC, additional 241 patients, in all participating oncology centers, could be treated. Occupation of infusion stations in chemotherapy sessions is a significant organizational and cost-effectiveness parameter because places occupied by patients represent the lost opportunity cost (not analyzed in this study), which prevents the optimal use of hospital infrastructure and does not allow it to generate additional income. In the study PHranceSCa [15], a randomized, open-label phase II study, the authors indicated that due to the reduced observation time for Pert/TrasSC, hospitals may avoid having too many patients in the hospital at the same time. This was an important factor in the COVID-19 pandemic as it reduced the risk of infection associated with visiting hospitals.

Our model also showed that with Pert/TrasSC, all patients in all participating oncology centers would spend a total of 3,345 hours in these hospitals, which is 8-fold shorter compared to the other regimens. Shortening the administration and observation time could significantly affect the quality of patients' lives. In a study by Jackisch C. et al. [14] patients preferred the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection into intravenous pertuzumab and trastuzumab due to time savings that had a positive impact on their daily life. The authors [14] also confirmed that Pert/TrasSC generated cost savings released capacity in chemotherapy units and significantly reduced intravenous compounding costs and waste. In PHranceSCa [12], patients preferred Pert/TrasSC because of the savings in time and feeling more comfortable during administration.

The main limitation of our study was the number of oncology centers participating in the questionnaire and the fact that only one hospital treated patients with all possible treatment regimens.

Conclusions

In our study, we created a model-based cost-minimization analysis to estimate non-drug-related costs differences between treatment with pertuzumab and trastuzumab in HER2-positive breast cancer in Poland. The model shows that Pert/TrasSC treatment was associated with significantly lower labor costs for nurses and pharmacists and lower costs of non-drug consumables. In addition, it reduced the length of hospital stay due to shorter administration and

observation times, which directly improved patients' quality of life. This benefit also released capacity at chemotherapy infusion sites, allowing more patients to be treated in the hospital. Our analysis showed that the non-drug cost differences between Pert/TrasSC, PertIV + TrasIV, and PertIV + TrasSC were always in favor of Pert/TrasSC.

Article Information and Declarations

Data availability statement

Original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Ethics statement

The method of data collection for the model (survey) eliminates the need for an ethical assessment of the published results.

Author contributions

M.S.: conceptualization, survey conducting, planned the cost minimalization model and drafted the manuscript, writing, all work coordinator; T.B.: resources, data curation, collecting data, critical revision of data, support in clinical aspects; J.A.: participated in the design of the model, critical revision of data; A.L.: writing, review and editing the manuscript, critical revision of data; P.M.P.: participated in the critical revision of the manuscript, support in clinical aspects

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Conflict of interest

M.S.: owner of a consulting company implementing pharmaco-economic projects for Roche.

P.M.P.: travel grants, speaker fees, clinical trials for Roche.

Other authors declare no conflict of interest.

Supplementary material

None.

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