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Home-based treatment with subcutaneous trastuzumab: safe and acceptable not only during a pandemic — final analysis of the RWD project 'FlexCare'

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ABSTRACT

Introduction. Trastuzumab shows similar efficacy and safety profile regardless of IV or SC administration. Subcutaneous administration enables reduction of treatment costs and time as well as equipment savings and is more convenient for both patients and healthcare providers. In Poland, home-based programs of treatment with biological drugs are already implemented; however, to date they do not include trastuzumab in BC patients. The project aimed to evaluate the organizational and therapeutic procedures related to home-based treatment with subcutaneous trastuzumab and satisfaction of patients and healthcare providers based on RWE.

Material and methods. Early HER2(+) BC patients treated with trastuzumab were enrolled in the study. Monitoring and duration of treatment were consistent with the summary of product characteristics (SmPC) and reimbursement rules. The first 3–6 doses of trastuzumab were administered at the cancer center, followed by home doses. Medical visits took place every 3 months. The data were analyzed using descriptive statistics. A positive opinion of the Bioethics Committee was obtained.

Results. Twenty patients participated in the project. The median age was 59 years (36–72 years). The average distance from the place of residence to the hospital was 24 km (2–65 km). We administered 232 doses, with an average of 11.6 doses per patient (range 6–14). The tolerance of trastuzumab was good and consistent with the SmPC. The average duration of a nurse's stay at home was 60 minutes. Almost all patients (19/20) appreciated the possibility of saving time and continuing their professional work as well as avoiding crowds and the risk of infection in the hospital. Two patients felt that nurse visits violated their privacy. No logistical or technical problems were observed.

Conclusions. Home-based treatment with subcutaneously administered trastuzumab is safe and easy to organize, positively perceived by both patients and nurses. It can be particularly important for disabled patients who have difficulty reaching the hospital, as well as for professionally active patients.

Key words: trastuzumab, subcutaneous use, home-based treatment, breast cancer

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Introduction

HER2-positive (HER2+) disease accounts for 15–20% of all breast cancers and is characterized by overexpression of the human epidermal growth factor receptor type 2 (HER2) and/or amplification of the coding gene [1]. Positive HER2 expression is a prognostic factor (associated with a worse prognosis) as well as a predictive factor — drugs that inhibit the HER2 signaling pathway have been developed [2]. The first drug that significantly improved the treatment outcomes in patients with HER2-positive breast cancer was trastuzumab [recombinant humanized IgG1 (immunoglobulin IgG1) monoclonal antibody binding to the extracellular domain of the HER2 receptor] [3]. Since its discovery at the end of the 20th century, other drugs have been developed that target the HER2 signaling pathway. The ones that are currently available include small-molecule tyrosine kinase inhibitors (lapatinib, neratinib, tucatinib), another monoclonal antibody (pertuzumab), and conjugates of antibodies and cytotoxic drugs (trastuzumab emtansine, trastuzumab deruxtecan, trastuzumab duocarmazine) [4–10]. Further drugs are the subject of ongoing clinical trials, which are in various phases.

The current standard of adjuvant systemic treatment in patients with early HER2-positive breast cancer includes the use of chemotherapy in combination with biological therapies targeting HER2 receptors. Biological treatment includes one year of trastuzumab, and in selected clinical cases, additionally pertuzumab and trastuzumab emtansine in patients with residual disease [11–13]. Compared to chemotherapy alone, this therapy significantly reduces the risk of disease recurrence and death and is in line with the guidelines of scientific societies [14].

Trastuzumab can be used in the intravenous form (infusion lasting 30–90 minutes) as the original drug (Herceptin®) or biosimilars, and in the subcutaneous form (injection 2–5 minutes), available only as the original preparation (Herceptin SC®). In a multicenter open-label randomized non-inferiority phase III clinical trial, no differences regarding efficacy and safety profile were found between these two forms of drug administration [15, 16]. On the other hand, a benefit was demonstrated in terms of reduction of treatment costs, saving time and equipment, as well as human resources when using the subcutaneous form compared to the intravenous form [17, 18]. The subcutaneous form is preferred by patients and medical staff as a more patient-friendly treatment, and it significantly shortens the patient's stay in the outpatient clinic or hospital [19].

The subcutaneous form of the drug in disposable applicators self-injected by the patient was also evaluated. Due to the costs of production and disposal, applicators were not used in everyday practice, but they were very positively assessed by patients and staff [20].

Subcutaneous trastuzumab may also be an attractive drug for home administration. In recent years, there has been a systematically increasing interest in the use of various forms of anticancer treatment at the patient's home (including oral and intravenous chemotherapy administered with the use of infusors), which improves patients' comfort, saves time and medical staff resources, and reduces the burden on the medical facilities [21–23]. Legal regulations in this area are being extended. The pandemic has highlighted the need for more flexible forms of treatment that can also be cost-effective and has accelerated their implementation. In Poland, trastuzumab has not been administered in everyday practice at home so far, although this form of treatment is used worldwide [24].

Aim of study

The FlexCare project aimed to collect information and evaluate organizational procedures during treatment with subcutaneous trastuzumab at home and in the treatment room (as part of nursing advice) and to assess patients and staff's satisfaction and sense of security.

Material and methods

The project was conducted in two comprehensive cancer centers in Poland, the Opole Oncology Center in Opole and the Podkarpacki *Oncological* Center in Brzozów, during the COVID-19 pandemic from December 2020 to December 2021. The inclusion criteria included

- written informed consent;
- age > 18 years;
- meeting the inclusion criteria for treatment in the drug program B.9 (PL B.9) in the version applicable during the project;
- adjuvant treatment with subcutaneous trastuzumab in monotherapy (after prior administration of the drug in combination with chemotherapy);
- absence of serious concomitant diseases;
- normal bone marrow, kidney, and heart function [left ventricular ejection fraction (LVEF) ≥ 50% in accordance with the requirements of the drug program];
- at least 3 drug administrations so far;
- no significant trastuzumab-related adverse events so far.

The treatment was conducted in accordance with the SmPC of the originator medicine. Eligibility for treatment, monitoring, and treatment duration were in line with PL B.9. The first 3–6 doses of the drug were administered in an oncology center in stationary or daily care mode. During the project, Herceptin SC® was administered at the patient's home or in the treatment

Figure 1. Nursing kit

room, and stationary medical visits took place on the day of scheduled monitoring visits (including laboratory and cardiological tests following PL B.9. treatment monitoring recommendations) and in every medically justified situation. Both in the case of administration at home and in the treatment room, a doctor (researcher) conducted a teleconsultation.

Trastuzumab was administered by a qualified nurse experienced in using the drug and trained in the management of allergic reactions. The nurse transported trastuzumab in a cooler bag and was equipped with a basic set of drugs to be used in the case of a hypersensitivity reaction and a set for medical waste disposal (Fig. 1). The assessment of the patient's condition before drug administration was conducted by the nurse according to a prepared questionnaire (taking medical history regarding well-being and measurements of basic vital signs). The course of the visit (interview, drug administration, post-injection observation) was reported by the nurse in appropriate questionnaires and communicated to the doctor over the phone. The time of patient observation after drug administration was intended for an educational talk.

Data were analyzed using descriptive statistics. Quantitative variables were expressed as mean, median, and range, and qualitative variables as sample numbers and percentages.

A positive opinion of the Bioethics Committee at the Opole Medical Chamber was obtained, as well as financial support from Roche, which provided the study drug free of charge.

Results

The project involved 20 female patients diagnosed with HER2+ early breast cancer. Four patients who were offered participation in the project declined (one due to concerns about the safety of the procedure and the others due to privacy concerns).

The median age of patients was 59 years (range 36–72 years). Seven women (35%) were professionally active, but as many as 50% were in pre-retirement age.

The average distance from the place of residence to the hospital was 24 km (range 2–65 km). All patients cooperated, were in proper contact, and, in their self-assessment, were independent in everyday activities. Only one patient reported mobility limitations due to degenerative joint disease.

A total of 232 doses were administered, corresponding to 11.6 doses per patient (range 6-14 doses). The majority of applications (57%) took place at home (Tab. 1).

The overall tolerability of trastuzumab was good and consistent with the SmPC. One patient (5%) discontinued therapy prematurely due to a decrease in left ventricular ejection fraction, and the remaining patients completed treatment as planned. All patients completed a satisfaction questionnaire. Almost all (95%) appreciated saving time, the ability to continue working, avoiding hospital crowds and the risk of infection. Almost all patients (90%) would recommend a home-based form of drug administration, but every tenth considered that the nurse's visit disturbed their privacy. No patient reported negative opinions, even though such a possibility was included in the questionnaires (I feel isolated/lonely with my disease; I am afraid of complications and that something will happen; it interferes with my privacy; there is no doctor nearby who gives me a sense of security). The patients also positively assessed drug administration in the treatment room combined with nursing advice. They emphasized a significantly shorter stay in the facilities compared to standard medical visits. One patient preferred administration in the treatment room but did not justify her choice, and the remaining patients preferred administration at home.

Three nurses participated in the project. The median subcutaneous injection time was 4 minutes (range 3–6), and the nurses' home visits lasted 55 minutes (range 30–130 minutes). Logistical and technical problems were not observed. Twice a nurse was waiting for the patient. Mild pain was reported during 12/232 applications (5%), and redness at the application site was observed after 9/232 applications (4%). Side effects did not extend the injection time and did not stop subsequent home administrations.

The nurses emphasized the value of health education of patients during these visits (maintaining proper body weight, regular physical activity, and not using

Table 1. Number of trastuzumab administrations

	Number of administrations	At home	In the office
Total	232	133	99
Per person	11.6	6.65	4.95

stimulants). The nurses emphasized the benefits for the treated women, mainly saving time and reducing the risk of infections. However, they noted the excessive amount of medical documentation that needed to be completed during home visits. The nurses highly appreciated the implementation of treatment in the nursing office and giving advice, which was a source of novel learning and experience as well as professional prestige for them.

Discussion

Self-administration of subcutaneous biologics is a common procedure in patients with diabetes, rheumatoid arthritis (RA), multiple sclerosis, and hemophilia [25]. The concept of home-based cancer treatment is also not new. Several studies have evaluated the possibility of administering cytotoxic and biological drugs at home [26–28].

In Poland, there are home-use programs for biological drugs. An example is the treatment of RA patients with tocilizumab [29]. Tocilizumab, a humanized IgG1 monoclonal antibody directed against the human interleukin 6 (IL-6) receptor, is administered subcutaneously using a single-use pre-filled syringe and a safety needle. A doctor starts the treatment. After appropriate instruction, the patient performs the first injection under the supervision of qualified medical staff, and the next injection can be performed independently at home. The patient's parent/guardian can also do this. The drug is administered weekly, and the patient reports every 3 months (with drug packages) for monitoring visits, during which the effectiveness and tolerability of treatment are assessed.

As part of the National Hemophilia Treatment Program, it is possible to self-administer at home emicizumab, a humanized monoclonal antibody, as a prophylaxis of bleeding episodes in patients with hemophilia A [30]. Before starting emicizumab, the patient is educated by the attending physician on the rules of drug taking (including injecting the precisely calculated dose and adherence to the injection timing regime, as well as potential side effects associated with the use of emicizumab and interactions with other drugs). The patient collects the drug, administers it subcutaneously at home and brings the used packaging to the treatment center.

To our knowledge, FlexCare is the first project in Poland to assess the possibility of home treatment with subcutaneous trastuzumab. The results of the FlexCare study highlight the benefits for patients and nurses in the subcutaneous use of the drug. Since each patient had previously received several doses of the drug in the hospital during a one-day stay, they could compare both procedures. Home administrations were quick, taking less than 5 minutes in most cases, with the entire procedure taking less than an hour. Few side effects were observed, and almost all patients would recommend this form of treatment. The nurses reported that organizational problems were rare, and visits provided professional satisfaction. The reported side effects were minor, did not extend the duration of injection, and did not result in excluding patients from the project. The nurses reported more adverse events than patients — perhaps because of the severity of the disease, adverse events were less important for the patients than for the nurses, and because the patients had become accustomed to pain during treatment [31]. Detailed analysis of the results (data not included) showed no difference in the perception of side effects depending on the number of injections given at home.

No organizational problems were observed during the project. The cold chain was preserved, and the importance of proper storage of biological drugs and the creation of conditions identical to those existing in oncology centers should be emphasized. Only three nurses participated in the project, which probably facilitated quality control and adherence to procedures.

The follow-up time after drug administration was respected. During the project, a post-authorization change to the SmPC of the original drug was made — the observation time after drug administration was reduced from 120 to 30 minutes, which was also introduced in the FlexCare project.

The FlexCare project was an example of the growing popularity of initiatives that reduce the burden of patients traveling to cancer centers. Moving treatment closer to patients or even to their homes by setting up satellite centers or mobile offices increases the possibilities of therapy and is accepted. This project also showed that anti-cancer biological treatment could be partially implemented by qualified nursing staff. Data from clinical trials show that, compared to intravenous administration, subcutaneous trastuzumab is preferred by patients, saves time for medical staff, shortens the time of drug preparation and administration, and reduces direct and indirect costs [19]. In this context, trastuzumab is well suited for implementation in various flexible forms of care.

In the Belgian BELIS study, a similar treatment plan was implemented — trastuzumab was administered intravenously in a daily ward, then subcutaneously in a day hospital, and finally subcutaneously at home [32]. The results of this study show that home use of trastuzumab is feasible and preferred by patients. In numerous programs and pilot studies in Europe, it was found that subcutaneous trastuzumab can be safely used at home, in primary care facilities, or local hospitals [31, 33–36]. These programs require planning, training, careful selection of patients, and good cooperation of medical staff at various levels as well as the creation of remote care systems. They can lead to an improvement in the quality of life of patients and reduce the financial burden on the system. The concepts of flexible care turned out to be particularly important during the COVID-19 pandemic, but it is worth implementing them regardless of the epidemic situation.

In recent years, a subcutaneous form of a combination preparation — trastuzumab and pertuzumab — has been approved for marketing. A phase III study confirmed its efficacy, safety, and pharmacokinetics compared with separately administered intravenous forms of both antibodies [37]. Patients also prefer the subcutaneous preparation of both drugs [38]. A study is currently underway in the United States evaluating home treatment with subcutaneous trastuzumab and pertuzumab [28]. There are also studies evaluating subcutaneous forms of other anti-cancer biological drugs.

The discussed project confirms the feasibility of implementing subcutaneous trastuzumab treatment at home. It is possible to conduct this medical procedure as part of standard oncological care. The treatment is safe and allows for a high level of patient and staff satisfaction. It helps patients to maintain professional activity and can be extremely valuable in the case of patients with limited mobility, for whom access to the treatment center is an insurmountable obstacle. The development of the discussed procedure should be considered as an additional form of treatment for patients with HER2-positive breast cancer. In our opinion, it would be a very valuable alternative. The project also showed that the standard course of treatment recommended by an oncologist could be performed independently by qualified nurses. We think that further organizational steps are possible to introduce nursing advice in oncology and implement selected procedures by qualified oncology nurses (closer to the patient's place of residence) after prior patient qualification by the oncologist in charge.

The strength of this study is its prospective nature, while the limitation — the small number of patients, implementation in only two centers, and the declarative nature of data collection. It would, therefore, be interesting to extend the project to other centers and include patients with advanced disease.

Treatment of breast cancer patients with trastuzumab has a long history. The side effect profile is well known and described. Making treatment delivery more flexible represents progress and may benefit the system.

Conclusions

Subcutaneous use of trastuzumab at home is safe and easy to organize and well-received by patients and staff. This form of treatment organization should be popularized, as it helps to free up hospital resources. It can be valuable for disabled patients with limited access to hospitals and for professionally active people. An educated nurse can conduct part of the chronic treatment with trastuzumab independently, relieving the doctor's workload. Real-world data can help to introduce this additional care option.

Article Information and Declarations

Data availability statement

All analyzed data is included in this article. Further inquiries may be directed to the corresponding author.

Ethics statement

A positive opinion was obtained from the Bioethics Committee at the Opole Medical Chamber in Opole

Author contributions

B.R.: should be considered the major author; author of the concept, methods, research (treatment and follow-up of the patients), data analysis, manuscript preparation.
J.H.-K.: author of the concept, methods, research (treatment and follow-up of the patients), manuscript preparation.
D.S., J.Sarga, B.N., G.S., J.Sawicka: treatment and follow-up of the patients
E.D.: author of the concept, methods
N.O.: follow-up of the patients, data analysis
P.Z.: follow-up of the patients, data analysis, manuscript preparation

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Conflict of interest

B.R.: received honoraria from Amgen, AstraZeneca, BMS, Gilead, Lilly, Novartis, Pfizer, Pierre-Fabre, Roche, Servier unrelated to the article.
J.H.-K.: received honoraria from: Lilly, Novartis, Roche unrelated to the article.
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