

The Efficacy of Software to Help Patients Understand Drug for Adjuvant Treatment for Breast Cancer: A Pilot Randomized Controlled Trial

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We assessed the usefulness of ChemoCalc, a software package for calculating drug costs, in helping patients understand these costs. We randomly assigned, in a 1 : 1 ratio, 20 women who had undergone surgery for early breast cancer to a group that discussed adjuvant treatment with their physicians using the ChemoCalc software (ChemoCalc group) or a group that discussed adjuvant treatment without ChemoCalc (Usual Explanation group). The participants completed a five-grade evaluation questionnaire after these discussions. The primary endpoint was the intergroup comparison of the questionnaire scores regarding participants' understanding of their treatment-associated drug costs. Median age was not significantly different between the ChemoCalc group and Usual Explanation group (57 vs. 50, respectively; $p=0.27$). Patients in the ChemoCalc group had a significantly higher perceived level of understanding of the drug cost than those in the Usual Explanation group (5 [4-5] vs. 2.5 [1-5], respectively; $p=0.002$). Scores related to the patients' perception that understanding drug costs is an important part of breast cancer treatment were also higher in the ChemoCalc group than the Usual Explanation group (5 [2-5] vs. 3 [1-5], respectively; $p=0.049$). ChemoCalc was found to be useful for understanding drug costs.

Key words: breast cancer, drug costs, ChemoCalc

The optimal therapy for women with breast cancer is determined based on the cancer subtype, with different subtypes responding better to adjuvant endocrine therapy, chemotherapy, or anti-HER2 agents [1-3]. In metastatic scenarios, treatment is similarly determined based on subtypes. Owing to new drugs, such as aromatase inhibitors and trastuzumab, the prognoses for patients with recurrent breast cancer have improved over time for hormone-receptor-positive and/or human epidermal growth factor receptor type 2-pos-

itive breast cancer [4,5]. Moreover, new agents such as pertuzumab, trastuzumab emtansine, fulvestrant, mammalian target of rapamycin inhibitors, and cyclin-dependent kinase 4/6 inhibitors can be used, and will continue to provide patients with further treatment options.

Although new drugs which can lead to improved prognoses for cancer patients have been developed, these drugs can be extremely expensive. Indeed, cancer treatments can be "financially toxic," as high out-of-pocket medical costs are associated with lower quality of

life and/or delayed or forgone care, and lead to an increased risk of adverse health outcomes [6, 7].

Shared decision-making is a process in which the clinician and patient jointly participate in a health decision after discussing the options and potential benefits and disadvantages, while considering the patient's values [8]. This discussion also includes financial issues related to treatment. Although the importance of communicating costs has been reported, rarely do discussions on this topic actually take place [9]. Barriers to cost-related discussions include uncertainty about prices, uncertainty about cost-sharing arrangements, and insufficient training of medical personnel.

In this context, an investigation into the efficacy of ChemoCalc (Nippon Chemiphar, Tokyo; https://www.nc-medical.com/chemiphar_oncology/chemocalc.html)—freely downloadable software for calculating drug costs—in helping patients and their physicians to understand treatment-associated drug costs would be of benefit. To date, no such analysis has been reported. We conducted this pilot study to explore the software's effectiveness for female breast cancer patients.

Patients and Methods

Patients. This study was approved by the Nagasaki University Hospital Clinical Research Ethical Committee (registration number 17112001), and all patients provided informed consent. Eligible patients

were women with early breast cancer, 20 years of age or older, who had undergone surgery for their cancer, and who had yet to discuss adjuvant therapy. Patients who had undergone neoadjuvant treatment were excluded.

ChemoCalc use (Fig. 1). The patient's share of medical expenses is determined by his or her age and income in Japan. A co-payment of 10%, 20%, or 30% of the medical costs is required, though maximum levels exist. For patients undergoing cancer treatment, a physician enters the patient's height and weight into the ChemoCalc software, which then calculates the body surface area (Fig. 1A). The regimen is then selected (Fig. 1B shows the selection of an epirubicin regimen), and the full cost of the anticancer drugs and antiemetics—as well as 10%, 20%, and 30% of those costs—is given. ChemoCalc also calculates the costs of endocrine therapy, molecular target therapy, antiemetic drugs, and granulocyte colony-stimulating factor.

Study design. This was a prospective, single-center, pilot randomized controlled study. Twenty patients were recruited at Nagasaki University to participate in the study from December 2017 to August 2018. After the physician received the patients' consent, the patients completed a questionnaire including the State-Trait Anxiety Inventory (STAI) [10]. The STAI is a commonly used measure of trait and state anxiety. It has 20 items for assessing trait anxiety and 20 for assessing state anxiety. All items are rated on a 4-point scale. Higher scores indicate greater anxiety.

A

BSA

Height : cm

Weight : kg

Body surface area : m² (Du Bois method)

Calculate Endocrine therapy Information of drug

B

FEC
EC
AC
DOC
Her+DOC
TC
PTX
PTX+BV
w Her+PTX
HAL
Per+Her+DOC
Per+Her+HAL
nabPTX
VNR
T-DM1
Her+VNR
GEM
Her+TC
Lapa+Cape
oral 5-FU analogues
Endocrine
★ Option
G-CSF
Antiresorptive drug

Result of drug cost -EC regime-

Height : 155 cm

Weight : 48 kg

BSA : 1.442 m² (Du Bois method)

Anticancer drug (Full Dose: Du Bois method)

CPA(600mg/m²): 865 mg/body 865 mg/body

EPI(90mg/m²): 129.8 mg/body 129 mg/body

Tri-weekly

CPA :
100mg 1bottle × 0
500mg 1bottle × 2

EPI :
10mg 5mL 1bottle × 3
50mg 25mL 1bottle × 2

Antiemetic

Alox 0.75mg iv 1 Bottle

Aprepitant 80mg 2 Capsule

Aprepitant 125mg 1 Capsule

Cost of CPA 2,508 yen

Cost of EPI 26,719 yen

Amount of drug cost 55,716 yen

30% of drug cost **16,715** yen

20% of drug cost **11,143** yen

10% of drug cost **5,572** yen

Fig. 1 ChemoCalc (original Japanese translated to English). Can be downloaded or used on the web for free. I obtained reprint permission. **A**, Title page of ChemoCalc; **B**, Drug cost for a patient who is 155 cm in height and 48 kg in weight, using an epirubicin regime.

Based on the scores, we categorized patients as having higher anxiety (45-80) or lower anxiety (20-44). Eligible patients were randomly assigned to discuss adjuvant treatment with their physicians using the ChemoCalc software (ChemoCalc group) or to discuss adjuvant treatment without ChemoCalc (Usual Explanation group) in the discussion. Patients within each group were stratified by their STAI scores. In the ChemoCalc group, the physician took part in shared decision-making regarding adjuvant therapy using pathological data, prognosis data (PREDICT v2.1 tool), and ChemoCalc. In the Usual Explanation group, the physician took part in such decision-making using only the pathological data and prognosis data (PREDICT v2.1 tool). The same physician conducted all such discussions. The physician usually did not explain the drug cost, and so the Usual Explanation group did not receive the drug cost without using the description provided by the drug manufacturer. After the discussion, the patients completed a five-grade evaluation questionnaire (Table 1). Higher scores indicated a higher degree of agreement with the question content.

Study end points. The primary endpoint was the comparison of the 2 groups' questionnaire scores regarding the patients' perceived level of understanding of the drug cost (Table 1, question 2). The secondary end points were other scores from the questionnaires. Finally, because explaining the use of ChemoCalc and the drug costs represents a potentially burdensome time expenditure for physicians, we calculated the total discussion time.

Statistical analysis. Respondents' clinicopathological features and questionnaires were compared between the ChemoCalc and Usual Explanation groups. Variables were provided as frequencies for categorical variables and median and interquartile ranges for quantitative variables. Associations between variables were assessed using Fisher's exact test for categorical variables and the Mann-Whitney U test for quantitative variables. All statistical analyses were performed with EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for the R (version 2.13.0, The R Foundation for Statistical Computing) environment; more precisely, it is a modified version of R Commander (version 1.6-3) including statistical functions frequently used in biostatistics [11]. Values of $p < 0.05$ were considered statistically significant.

Results

Patients. A total of 20 female Japanese breast cancer patients, with ages ranging from 32-71 years, were recruited (Fig. 2). Ten were assigned to the ChemoCalc group and 10 to the Usual Explanation group (Table 2). Patient characteristics are shown in Table 2. Although the Usual Explanation group tended to be younger and to more of the patients have had chemotherapy than the ChemoCalc group, there were no statistically significant differences in any factors between the groups.

Comparison of questionnaire scores between the

Table 1 Questionnaire Items

| |
|---|
| 1. Did you feel comfortable about talking with the physician during the discussion? |
| 2. Do you understand the drug cost? |
| 3. Do you think the drug cost is important when deciding on adjuvant therapy? |
| 4. Are you worried about the drug cost? |
| 5. Do you understand the treatment choice? |
| 6. Do you understand the drugs' efficacy? |
| 7. Do you understand the drugs' potential adverse events? |
| 8. Do you have positive feelings about undergoing breast cancer treatment? |
| 9. Are you employed? |
| 10. (Only ChemoCalc group) Was ChemoCalc easy to understand? |

ChemoCalc and Usual Explanation groups (Table 3). The primary endpoint was defined as comparing the questionnaire scores for the patients' perceived level of understanding of the drug cost between the ChemoCalc group and the Usual Explanation group; the scores for the ChemoCalc group were significantly higher (ChemoCalc group vs. Usual Explanation group; 5 [4-5] vs. 2.5 [1-5], respectively; $p=0.002$). The scores representing the perception of patients that drug costs

are an important part of breast cancer treatment were also higher in the ChemoCalc group (ChemoCalc group vs. Usual Explanation group; 5 [2-5] vs. 3 [1-5], respectively; $p=0.049$). In contrast, no significant between-group differences were seen in the patients' understanding of drug efficacy, understanding of drug-related adverse events, or positive feelings toward treatment. Patients in the ChemoCalc group had high scores on the item stating that ChemoCalc was easy to understand. The discussion time needed for the explanation of another clinical trial was also not significantly different between the groups (ChemoCalc group vs. Usual Explanation group; 25 min [13-36] vs. 33 min [15-58], respectively; $p=0.10$).

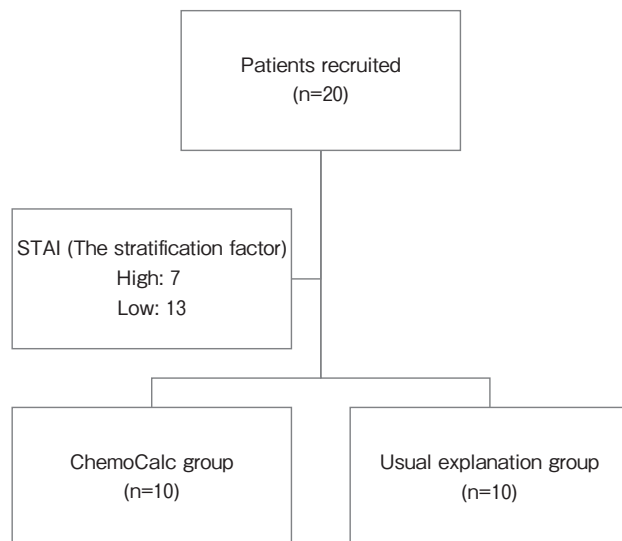


Fig. 2 Flowchart of patients.

Discussion

This report describes a pilot randomized controlled trial that was conducted to examine the efficacy of ChemoCalc in women with breast cancer who were making a decision regarding adjuvant treatment. Patients' perceived levels of understanding of drug costs and the importance of such costs were found to be higher in the group whose consultation included ChemoCalc.

Another report [12] found that the discussion of costs is a crucial component of clinical decision-making for a number of reasons. Discussing out-of-pocket costs

Table 2 Clinical Factors in Usual Explanation Group and ChemoCalc Group

| | Usual Explanation group | ChemoCalc group | P-value |
|--|-------------------------|-----------------|---------|
| Median age (range) | 50 (32-71) | 57 (48-67) | 0.27 |
| State-Trait Anxiety Inventory High/low | 3/7 | 4/6 | 1 |
| Breast surgery Mastectomy/Lumpectomy | 4/6 | 6/4 | 0.66 |
| Lymph node surgery Ax/SN | 1/9 | 1/9 | 1 |
| Subtype Luminal/Luminal HER2/HER2-enriched/TN | 8/1/1/0 | 9/1/0/0 | 1 |
| Endocrine therapy Yes/No | 9/1 | 10/0 | 1 |
| Chemotherapy Yes/No | 5/5 | 2/8 | 0.35 |

Ax, Axillary dissection; SN, Sentinel lymph node biopsy.

Table 3 Results of Questionnaire (Table 1)

| | Usual Explanation group | ChemoCalc group | <i>P</i> -value |
|--|-------------------------|-----------------|-----------------|
| 1. Comfortable discussion [#] | 5 (5–5) | 5 (4–5) | 0.37 |
| 2. Understanding of drug cost [#] | 2.5 (1–5) | 5 (4–5) | 0.002 |
| 3. Importance of drug cost [#] | 3 (1–5) | 5 (2–5) | 0.049 |
| 4. Worried about drug cost [#] | 3 (1–5) | 3.5 (1–5) | 0.79 |
| 5. Understanding of treatment choice [#] | 5 (5–5) | 5 (5–5) | 1 |
| 6. Understanding of drug efficacy [#] | 5 (5–5) | 5 (5–5) | 1 |
| 7. Understanding of drugs' adverse events [#] | 5 (4–5) | 5 (4–5) | 0.58 |
| 8. Positive feelings about treatment [#] | 5 (3–5) | 5 (4–5) | 0.58 |
| 9. Employed Yes/No | 7/3 | 6/4 | 1 |
| 10. Ease of understanding ChemoCalc | | 5 (4–5) | |
| Median discussion minutes (range) | 33 (15–58) | 25 (13–36) | 0.10 |

[#]These scores were median and range.

enables patients to choose lower-cost treatments when viable alternatives are available. Such discussions may also assist patients who are willing to trade off some chance of medical benefit in return for less finance-related distress. Additionally, discussing such costs can benefit patients by enabling them to seek financial assistance early enough in their care to minimize financial distress. Furthermore, a growing body of evidence suggests that including a consideration of costs in clinical decision-making may reduce costs for patients and society in the long term [12]. In fact, one report on bladder cancer patients showed that patients struggling with finances experienced worse physical and mental health, and lower cancer-specific health-related quality of life, physical well-being, and functional well-being [13]. The American Society of Clinical Oncology (ASCO) advocated a conceptual framework for assessing the value of cancer treatment options. Through its Value in Cancer Care Task Force, ASCO defines value in cancer care by emphasizing clinical benefit (efficacy), toxicity (safety), and cost (efficiency). This framework enables beneficial conversations between physicians and patients about the value of a new therapy over an accepted standard [14].

A survey of needs in the cost conversation found that 63% of patients and 79% of physicians wanted to discuss patients' out-of-pocket costs, though only 15% of patients and 35% of physicians did so [9]. Another

report found that breast cancer patients wanted to discuss the costs of care [15]. This raises the question of why patients and physicians often fail to have conversations about costs when they both report that they want to. Reported barriers to discussing out-of-pocket costs with patients include the premise that an ethical physician should not withhold beneficial treatments because of cost, uncertainty about prices, uncertainty about cost-sharing arrangements, and insufficient training [16,17]. In Japan, patients' co-payments are determined based on their age and income—10%, 20%, or 30% of the full medical costs—though maximum levels exist, and almost all patients are aware of what their co-payments will be. ChemoCalc calculates 10%, 20%, and 30% of the entire drug cost. In this pilot study, ChemoCalc enabled patients to easily understand drug costs while not requiring a great deal of their physician's time. Previous surveys have examined the needs or the importance of cost conversations, but there have been no interventional studies on overcoming the cost communication barrier. The present study shows, and further studies will elaborate, that the barrier of uncertainty about prices can be overcome. Physicians should seek to overcome barriers in cost communication to achieve true shared decision-making.

Among the participants in this study, more subjects in the ChemoCalc group than in the Usual Explanation group expressed the opinion that drug cost was an

important consideration in their treatment. Because patients in the latter group may not have understood the costs, they may not have realized their importance. Previous research suggests that high out-of-pocket costs are associated with medication nonadherence [18]. We have reported that Japanese women with breast cancer have high adherence to adjuvant endocrine therapy [19,20], and we can add that patients who start adjuvant therapy without understanding drug costs may be more likely to be nonadherent. Participants in the present study for whom adjuvant chemotherapy was recommended had less anxiety about drug costs, which may be related to the anxiety about the side effects of chemotherapy being a higher priority than cost anxiety.

Our study had some limitations. First, because we enrolled patients who had undergone surgery for their cancer, but who had yet to discuss adjuvant therapy, we excluded patients who had undergone neoadjuvant chemotherapy. At our institution, we recommend neoadjuvant treatment for patients with the HER2-positive and triple-negative subtypes. Because of this, only three patients with HER2-positive disease and only 7 patients who received chemotherapy were enrolled in this study. Chemotherapy and anti-HER2 drugs are more expensive than endocrine therapy; therefore, future studies should include patients who undergo neoadjuvant chemotherapy. Second, as we sought to investigate the usefulness of ChemoCalc in helping patients understand drug costs, we enrolled only patients without metastasis. Because high-cost drugs are mainly used in a metastatic setting, patients with metastatic disease should also be included in future studies. Third, because this was a pilot study, we did not pursue whether there were differences in treatment choices and compliance. That is a topic to explore in future studies.

This study revealed that the use of ChemoCalc software greatly improved female breast cancer patients' perception that they could understand the cost of drugs, and without a large time commitment for the participating physician. We plan to conduct a multicenter phase 2 randomized controlled study to further explore the usefulness of ChemoCalc and how it affects physician-patient discussions.

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