Patient Preference and Adherence

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ORIGINAL RESEARCH

Preferences for oral versus intravenous adjuvant chemotherapy among early breast cancer patients

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Purpose: The purpose of this study was to evaluate preferences for oral versus intravenous adjuvant chemotherapy among early breast cancer patients (UMIN-CTR number UMIN000004696).

Patients and methods: Eighty-two postmenopausal women with estrogen receptor-positive, human epidermal growth-factor receptor 2-negative breast cancer who had completed adjuvant chemotherapy were asked about their preferred route of administration of chemotherapy and the reason. Women also answered questions about their physical and psychological status and quality of life during chemotherapy.

Results: Patients who had received oral chemotherapy preferred it more frequently than those who had received intravenous chemotherapy (100% versus 37%, respectively, chi-square =15.5; $P<0.001$). Patients who preferred the same route of administration of chemotherapy as they had previously received showed a significantly better psychological status during chemotherapy compared with those who preferred a different route.

Conclusion: Our study showed that preferences for oral and intravenous chemotherapy strongly depended on the actual prior administration of chemotherapy and patients' own experiences during chemotherapy.

Keywords: breast cancer, adjuvant, chemotherapy, patient preference, oral, intravenous

Introduction

Adjuvant chemotherapy for early breast cancer prolongs disease-free and overall survival.[1] Adjuvant chemotherapy for early breast cancer has historically relied on intravenous (IV) administration. However, over the past decade, increasing attention has been focused on the merits of oral therapy because of the development of novel oral anticancer drugs. Oral fluoropyrimidines, such as uracil–tegafur (UFT), have been widely used in Japan as postoperative chemotherapy for breast, gastric, and colorectal cancers, mainly because of the ease of administration.[2] Recently, two randomized controlled trials comparing UFT with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) for early breast cancer showed similar efficacy in terms of disease-free survival.[3,4] Combined analysis of these trials demonstrated that UFT is noninferior to CMF in terms of inhibiting the recurrence of estrogen receptor (ER)-positive, early breast cancer.[5]

CMF is no longer the standard adjuvant chemotherapy regimen for early breast cancer. Now, the mainstream of adjuvant chemotherapy for breast cancer is anthracycline- and taxane-based chemotherapy regimens. However, it is well known that breast cancer is a heterogeneous disease, and its response to chemotherapy strongly depends on the ER

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and human epidermal growth-factor receptor 2 (HER2) status of the primary tumors. Adjuvant UFT seems to show similar efficacy to CMF-, anthracycline-, or taxane-based regimens for ER-positive, HER2-negative breast cancer patients, for the following reasons.[5–7] Firstly, as mentioned above, UFT is similar to CMF in terms of the achieved disease-free survival of ER-positive, early breast cancer patients.[5] Secondly, a retrospective subgroup analysis of 1,322 node-positive patients in the Cancer and Leukemia Group B 9344 trial suggested that the benefits of paclitaxel were not noted in those with the ER-positive/HER2-negative phenotype.[6] Thirdly, Gennari et al[7] performed a pooled analysis of the interaction between HER2 status and efficacy of adjuvant anthracyclines based on randomized trials that compared anthracycline-based with non-anthracycline-based adjuvant chemotherapy regimens in the treatment of early breast cancer. In HER2-negative disease, anthracyclines did not improve disease-free or overall survival, compared with a non-anthracycline-containing regimen (almost a CMF regimen).

The expected benefits of treatment should be weighed against the potential risks, and patients' preferences should be carefully considered when selecting treatment. Profiles of adverse events are clearly different between oral and IV types of chemotherapy.[3,4] Adverse events of IV chemotherapy include hair loss, nausea, vomiting, general fatigue, and infection. On the other hand, these adverse events are rarely seen when using oral chemotherapy. Moreover, oral drug administration can spare visits to the clinic, or venipunctures. It is estimated that patient preferences have markedly influenced decision-making, particularly when the treatment options are very different in terms of treatment schedules and adverse events and each treatment is expected to have the same efficacy. Several studies have evaluated psychosocial factors in patients that determine the choice of a particular chemotherapy regimen. Several surveys have shown that most patients with cancer prefer oral to IV therapy.[8–11] Previous studies reported that reasons for preferring oral chemotherapy were convenience and a dislike of needles.[8,9] However, the assumption that early breast cancer patients significantly prefer the oral route of chemotherapy administration has not been formally tested in an adjuvant setting.

The purpose of this study was to evaluate preferences for oral versus IV adjuvant chemotherapy among early breast cancer patients.

Patients and methods

Participants were early breast cancer patients who visited Osaka Medical Center for Cancer and Cardiovascular Diseases as part of their regular postoperative follow-up between December 2010 and December 2011. Eligibility criteria were as follows: 1) postmenopausal (at diagnosis) women with early breast cancer, whose tumors were ER-positive and HER2-negative; 2) patients who had previously received adjuvant chemotherapy; and 3) patients who had no evidence of recurrence at the time of participation. Patients who had received neoadjuvant chemotherapy were excluded. This study was approved by the institutional review board of Osaka Medical Center of Cancer and Cardiovascular Diseases.

Eligible patients were then directly approached by one of the investigators. If they showed an interest in the study, detailed information was provided, and patients were then approached for enrollment. Women completed the questionnaire and posted it to our hospital.

Participants were then read a hypothetical clinical scenario modified by those developed by Fallowfield et al[9,12]: "Imagine you were recently diagnosed with breast cancer and have already had surgery to remove the cancer. Next, you see a specialist who talks to you about two different follow-up treatments to prevent the cancer from coming back. Research has shown that each treatment is equally effective, but they have different side effects. You must decide which treatment to have. One treatment would be pills taken orally twice a day and you would continue to see your doctor for 2 years. Anticipated side effects of oral chemotherapy include liver dysfunction and skin/nail pigmentation. The other treatment would be administered intravenously once monthly at your hospital. You would continue to see your doctor for 3 to 6 months. Anticipated side effects of IV chemotherapy include nausea, vomiting, appetite loss, hair loss, skin/nail pigmentation, fever, peripheral neuropathy, and edema."

Each patient's treatment preference was then selected using three response options: oral, IV, or no preference. The reasons behind a patient's preference were assessed semiquantitatively using a series of Likert scale statements reported in Liu et al,[8] where 1 was "strongly agree," 2 was "somewhat agree," 3 was "undecided," 4 was "somewhat disagree," and 5 was "strongly disagree".

Participants also answered questions about their physical or psychological status and quality of life during chemotherapy using a 5-point Likert scale, where 1 was "very bad," 2 was "somewhat bad," 3 was "neutral," 4 was "somewhat good," and 5 was "very good."

Disease and treatment details were collected from participants' medical records, and this was approved by the institutional review board.

Data-analysis strategy

The association between the actual route of administration of chemotherapy with patient preferences was evaluated using the chi-square test. Subsequently, patients were grouped according to the combination of the actual route of administration of chemotherapy and patient preferences. The associations of these patient groups with physical and psychological status, and quality-of-life scores using the Likert scale were evaluated using Student's *t*-test. In addition, the association of patient preferences with the reasons using the Likert scale was assessed using Student's *t*-test. All of the statistical tests and *P*-values were two-tailed, and *P*-values of <0.01 were considered significant. All statistical tests were performed with SPSS 21 software (IBM, Armonk, NY, USA).

Results

A total of 101 women were approached for the study, and 82 (81%) completed the study questionnaire. Patient characteristics are shown in Table 1. Of the 82 patients surveyed, eleven (13%) had previously received oral chemotherapy, and 71 (87%) had previously received IV chemotherapy. There were no patients receiving both treatments. Representative doses of each chemotherapy regimen were as follows: CMF – 100 mg cyclophosphamide given orally on days 1–14 followed by a 14-day rest, 40 mg/m^2 methotrexate given intravenously on days 1 and 8, and 500 mg/m^2 fluorouracil given intravenously on days 1 and 8; anthracycline – 60 mg/m^2 epirubicin and 600 mg/m^2 cyclophosphamide; taxane – 75 mg/m^2 docetaxel and 600 mg/m^2 cyclophosphamide, anthracycline; and taxane – 500 mg/m^2 fluorouracil, 75–100 mg/m^2 epirubicin, and 500 mg/m^2 cyclophosphamide followed by 70 mg/m^2 docetaxel.

Of the 82 patients, 37 (45%) preferred oral chemotherapy, 29 (35%) preferred IV chemotherapy, and 16 (20%) patients had no preference. There were significant differences in preferences according to the actual prior route of administration of chemotherapy. Of the eleven patients who had received oral chemotherapy, all eleven (100%) preferred it. On the other hand, of the 71 patients who had received IV chemotherapy, only 26 (37%) preferred oral chemotherapy (χ^2=15.5, $P<0.001$, Figure 1). There were no significant differences in patient preference depending on the age (oral preference 63.0, IV preference 62.8, t=0.1; P=0.9).

Frequencies of patients who experienced dose reduction or early cessation of adjuvant chemotherapy due to adverse events were not significantly different between each patient group (oral preference 9%, IV preference 21%, χ^2=2.0; P=0.2).

Because there was a strong relationship between the actual prior route of administration of chemotherapy and patient preferences, patients were grouped into three categories

Table 1 Patient characteristics (n=82)

	Number of patients			
	All (n=82)	**Oral preference (n=37)**	**IV preference (n=29)**	**No preference (n=16)**
Age, years				
Median	63	63	63	60
Range	50–79	50–79	51–72	52–78
Stage				
I	6	4	1	1
II	54	24	20	10
III	22	9	8	5
Previous chemotherapy				
Oral				
Uracil–tegafur	10	10	0	0
Doxifluridine	1	1	0	0
IV				
CMF	10	2	5	3
Anthracycline	35	15	11	9
Taxane	8	2	5	1
Anthracycline/taxane	18	7	8	3
Period of diagnosis				
1995–1999	3	3	0	0
2000–2004	20	6	6	8
2005–2010	59	28	23	8

Abbreviations: IV, intravenous; CMF, cyclophosphamide, methotrexate, and 5-fluorouracil.

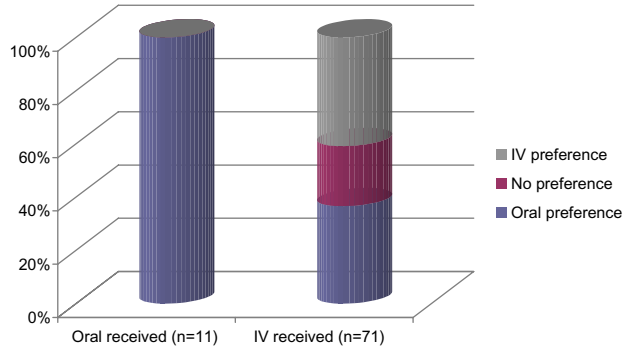

Figure 1 Association of actual route of administration of chemotherapy and patient preferences.
Note: The y axis indicates the proportion of patient preference according to the actual route of administration of chemotherapy.
Abbreviation: IV, intravenous.

according to the combination of the prior route and patient preferences: group A, patients who had received and preferred oral chemotherapy; group B, patients who had received and preferred IV chemotherapy; and group C, patients who had received IV and preferred oral chemotherapy. The association of the three patient groups with physical status, psychological status, and quality of life during chemotherapy is shown in Table 2. Patients in groups A and B showed a significantly more favorable psychological status during chemotherapy compared with those in group C (A versus C, t=2.8, P=0.009, B versus C, t=2.8, P=0.007). In addition, patients in group A had a significantly better physical status compared with those in group C (t=3.5, $P<0.001$). There were no differences between patients in groups A and B.

Figure 2 shows the association between patient preferences and reasons. Patients who preferred oral chemotherapy more frequently gave their reasons as relating to the place of treatment and anxiety over an IV line, compared with those who preferred IV chemotherapy (place of treatment, t=–10.4, $P<0.001$; anxiety over an IV line, t=–4.4, $P<0.001$). In contrast, patients who preferred IV chemotherapy more frequently gave their reasons as treatment duration and their feeling that it was more efficacious, compared with those who preferred oral chemotherapy (treatment period, t=6.1, $P<0.001$; IV would be more effective, t=4.1, $P<0.001$).

Table 2 Association of patient groups with physical status, psychological status, and quality of life during chemotherapy (n=66)

	Patient groups		
	Group A (n=11)	Group B (n=29)	Group C (n=37)
Physical status	3.6[a]	2.9	2.3[a]
Psychological status	3.3[b]	3.1[c]	2.3[b,c]
Quality of life	3.6	3.2	2.9

Notes: [a]t=3.5, $P<0.001$; [b]t=2.8, P=0.009; [c]t=2.8, P=0.007. Data on patients with no preference (n=16) were excluded. For physical status, psychological status, and quality of life, a higher score indicates a more favorable state. Group A, patients who had received and preferred oral chemotherapy; Group B, patients who had received and preferred IV chemotherapy; Group C, patients who had received IV but preferred oral chemotherapy.
Abbreviation: IV, intravenous.

Discussion

To the authors' best knowledge, the present survey study is the first to evaluate preferences for oral versus IV adjuvant chemotherapy among early breast cancer patients. Our study showed that patient preferences for oral and IV chemotherapy strongly depended on the actual received route of chemotherapy. All patients who had received oral chemotherapy preferred it. In contrast, less than half of patients who had received IV chemotherapy preferred this form. Our study also demonstrated that patients who preferred the actual route of administration (groups A and B) had a more favorable physical and psychological status during chemotherapy than those who did not (group C). These results indicate that patients' own experiences during chemotherapy strongly reflect their preferences for the chemotherapy route. High scores for physical and psychological status among patients who had received oral chemotherapy (group A) were consistent with previous reports of randomized controlled trials regarding quality-of-life assessment for patients who received adjuvant oral chemotherapy.[3,13] In our study, fewer patients (45%) preferred oral chemotherapy than those in published reports (63%–95%).[8–11] This is probably due to the small number of patients who had received oral chemotherapy among patients participating in this study.

The place of treatment and anxiety over an IV line were important reasons for selecting oral chemotherapy in this study. These reasons were consistent with previous reports.[8,9] In this study, common reasons for selecting IV chemotherapy were the treatment duration and the feeling that it is more efficacious. Fallowfield et al[12] analyzed patient preferences for CMF versus goserelin among premenopausal women with early breast cancer. In their report, one of the common reasons for preferring CMF was a shorter treatment duration, which was comparable with our study. Despite the fact that treatments were described as equally effective, patients who preferred IV chemotherapy felt that it was more efficacious. Similar findings were reported by Fallowfield et al.[9]

There are several strengths in our study. The response rate to our questionnaires was high (81%). Furthermore, the eligibility criteria of this study were limited to postmenopausal women with ER-positive, HER2-negative early breast cancer who had previously received adjuvant chemotherapy. Patients who met these criteria can select oral or IV chemotherapy

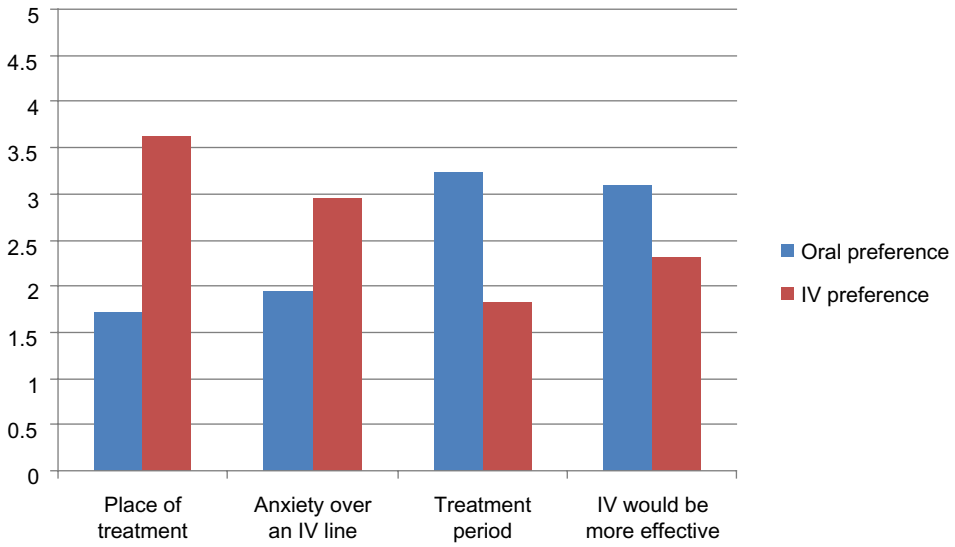

Figure 2 Reasons for oral or intravenous chemotherapy (ranked from strongly agree [1] to strongly disagree [5]).
Notes: The *y* axis indicates the reasons behind a patient's preference using a series of Likert scale (ranked from strongly agree [1] to strongly disagree [5]). Place of treatment, $t=-10.4$, $P<0.001$; anxiety over an IV line, $t=-4.4$, $P<0.001$; treatment period, $t=6.1$, $P<0.001$; IV would be more effective, $t=4.1$, $P<0.001$.
Abbreviation: IV, intravenous.

based on preference in the future. The results of this study may provide information to help patients and oncologists select from oral versus intravenous chemotherapy.

Study limitations

Limitations are the small sample size and the fact that the majority of women in our study had received IV chemotherapy and only eleven patients had received oral chemotherapy. Furthermore, there were no patients who had received both treatments. The lack of a patient cross-over is a major limitation for this study in its current form; therefore, this study cannot be used to make any definitive conclusions.

Because this study was retrospective, there was no predefined protocol for each chemotherapy regimen. In addition, we were not able to evaluate changes in preference over time, because questionnaires were obtained at one time.

The translation of the questionnaires originally written in English into Japanese in this study was not thoroughly validated. Also, because of the cross-sectional nature of this study, causality cannot be demonstrated.

In conclusion, our study showed that preferences for oral and IV chemotherapy strongly depended on the actual received route of chemotherapy and patients' own experiences during it. Our results provide information for improved selection of adjuvant chemotherapy for early breast cancer patients, especially in the situation where oral and IV chemotherapy show the same efficacy. Further studies regarding preferences for therapies other than chemotherapy, eg, targeted therapies, are warranted.

Acknowledgment

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Disclosure

The authors report no conflicts of interest in this work.

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