

Physicians' knowledge, attitude, and behavior regarding fertility issues for young breast cancer patients: a national survey for breast care specialists

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Abstract

Background Fertility is one of the key aspects of quality of life for breast cancer patients of childbearing age. The objective of this study was to describe fertility-related practice for young breast cancer patients in Japan and to identify healthcare provider factors that contribute to physicians' behavior towards fertility preservation.

Methods A cross-sectional survey was developed in order for Japanese breast cancer specialists ($n = 843$) to self-evaluate their knowledge, attitude, and behavior regarding fertility preservation. Survey items included questions regarding knowledge of and attitude toward fertility issues in cancer patients, fertility-related practice, potential barriers for the discussion of fertility with patients, and responding physicians' socio-demographic background.

Results Four hundred and thirty-four (52%) breast oncologists responded to the survey. Female and younger oncologists (age less than 50 years) had significantly higher probability of referring patients to reproductive

specialists. Physicians who had better knowledge score and positive attitudes toward fertility preservation were more likely to discuss potential fertility issues with cancer patients. This was significantly associated with consultation and referral to reproduction specialists when encountering fertility issues with cancer patients. Risk of recurrence, lack of collaborating reproductive specialists, and time constraints in the clinic were identified as major barriers to discussion of fertility preservation with breast cancer patients.

Conclusion Female and younger physicians as well as physicians working in a multidisciplinary environment had positive attitudes and behavior towards fertility preservation in breast cancer patients. The development of comprehensive and interdisciplinary programs for healthcare providers is necessary to meet the expectations and fertility needs of breast cancer patients.

Keywords Fertility preservation · Breast cancer · Survivorship

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Introduction

With improvement of cancer prognosis, fertility has become one of the key aspects of quality of life for breast cancer patients of childbearing age. Distress about interrupted childbearing is likely to persist in long-term female cancer survivors [1]. The American Society of Clinical Oncology (ASCO) has developed guidance for oncologists regarding available fertility preservation methods and related issues [2]: oncologists should address the possibility of infertility with patients during their reproductive years and be prepared to discuss possible fertility preservation options or refer appropriate and interested patients to

reproductive specialists as early as possible during treatment planning.

However, previous studies have shown that only 23% of the patients younger than 40 years of age were informed of potential infertility after cancer treatment in a single institution in Japan and less than half of oncologists were following the ASCO guideline in the USA [3, 4]. The practice of oncologists regarding fertility preservation in cancer patients of reproductive age may depend on multiple factors: the patient's medical and psychosocial condition [5, 6], the patient's knowledge [7], and physicians' knowledge about fertility preservation [8].

We have previously analyzed the decision-making process for adjuvant treatment in young breast cancer patients of reproductive age [3]. Significantly less patients expressed interest in fertility when they had children or advanced disease. Less aggressive treatment (without chemotherapy) was recommended by oncologists for patients who voluntarily expressed an interest in preserving fertility [3]. Nearly one-third of the patients who expressed an interest in fertility selected a different adjuvant treatment from the primary recommendation of the oncologist because of their concern for preserving fertility, whereas the majority of patients who did not express an interest in preserving fertility followed the oncologists' primary recommendation [3].

The awareness and attitude of patients in the clinic might reflect the ability of healthcare providers to provide an environment in which patients could bring up fertility issues. The objectives of this study include describing fertility-related practice for breast cancer patients in a variety of clinical settings in Japan and identifying healthcare provider factors that contribute to physicians' behavior regarding fertility preservation in young breast cancer patients.

Methods

Selection of participant

A cross-sectional survey was developed in order for board-certified breast oncologists of the Japanese Breast Cancer Society (JBCCS), who are the main physicians treating breast cancer patients in Japan, to self-evaluate their knowledge, perception, and behavior regarding fertility issues in young breast cancer patients.

Measures

The survey consisted of 49 items including questions regarding knowledge of and attitudes towards fertility in cancer patients, practice behavior of fertility-related discussions with patients, potential barriers for these

discussions, and demographic background of the practitioners (Table 1). Survey items were derived from existing literature and multidisciplinary discussion. Physicians were asked to evaluate their agreement with the statements using a five-grade system (1, strongly agree; 2, agree; 3, cannot decide; 4, disagree; 5, strongly disagree).

1. Knowledge about fertility issues in breast cancer patients

To evaluate the accuracy of knowledge about fertility issues in breast cancer patients, the statements were developed from the latest JBCCS treatment guideline [5]. For statements A-1 and A-4, the respondents were considered to have more accurate knowledge when the score was lower. For statements A-2 and A-3, the respondents were considered to have more accurate knowledge when the score was higher. Then the sum of $(5 - \text{"score for A-1"}) + (\text{"score for A-2"}) + (\text{"score for A-3"}) + (5 - \text{"score for A-4"})$ was calculated. The respondents with a higher sum were considered to have more accurate overall knowledge. A-5 was not used to evaluate the accuracy of knowledge because of lack of definite evidence, but correlated with the use of LHRH agonist for fertility preservation.

2. Practice behavior for breast cancer patients of reproductive age

Practice behavior statements consisted of 13 items including statements used in the US oncologist survey with some modifications to adapt to Japanese practice setting. The statements "I discuss the impact of cancer treatment on future fertility with my patients", "I consult reproductive specialists with questions about fertility issues in my patients", and "I refer patients who have questions about fertility to reproductive specialists" were considered the most important behavior according to the ASCO guideline [2].

3. Potential barriers for discussing fertility issues with breast cancer patients

Among seven potential barriers asked in the questionnaire, four were similar to statements used in the US survey [4]. We put three additional statements (patients' voluntary expression of interest, existence of spouse/partner, and support from co-medical staff) that were created by findings from our previous study [2] and by considering Japanese culture. In addition, we asked the participant to describe the greatest difficulty in discussing fertility in an open question.

4. Attitude towards fertility preservation of cancer patients

Five statements were selected from the US survey [4]. Because the hereditary aspect of breast cancer was considered to be not genuinely linked with perception of

Table 1 Questionnaire statements

A. Knowledge about fertility issues of breast cancer patients

1. Total dose of alkylating agents are related to infertility
2. Pregnancy after breast cancer increases risk of recurrence
3. Pregnancy after chemotherapy increases risk of deformity of the child
4. Pregnancy should be avoided during tamoxifen treatment
5. Luteinizing hormone releasing hormone (LHRH) analogue reduces the risk of chemotherapy-induced amenorrhea

B. Practice behavior

1. Patients voluntarily bring up the fertility issues in the clinic
2. I discuss the impact of cancer treatment to future fertility with my patients
3. I do not feel comfortable to discuss fertility issue with my patients
4. I take into account the history of childbirth when I discuss fertility issue with my patient
5. I take into account whether she has a spouse/partner when I discuss fertility issue with my patient
6. I take into account economical status of the patient when I discuss fertility issue with my patient
7. I discuss fertility issues with breast cancer patients with high risk of recurrence
8. Patients talk to co-medical staff about their concern about fertility
9. I ask co-medical staff if a patient has an interest in fertility
10. I provide my patients with educational material about fertility preservation
11. I use LHRH analogue to preserve fertility
12. I consult a reproductive specialist with questions about fertility issues in my patients
13. I refer patients who have questions about fertility to reproductive specialists

C. Barriers for discussing fertility issues

1. The patient does not express their interest in fertility
2. The patient has high risk of recurrence
3. The patient has economic problems
4. The patient does not have a spouse/partner
5. There is no place/person to refer my patients to for fertility preservation
6. Time constraints affect my ability to discuss fertility preservation
7. There is no support from co-medical staff
8. What is the greatest difficulty in discussing fertility issues with young breast cancer patients?

D. Attitude toward fertility preservation

1. Patients with poor prognosis should not pursue fertility preservation
2. Posthumous parenting is troublesome for bereaved family
3. Losing mothers will negatively affect bereaved children
4. I fear passing hereditary cancer to a biological child
5. Treating cancer is more important than fertility preservation

E. Demographics and medical backgrounds

1. What is your gender?

Table 1 continued

2. What is your age?
3. What is your religious background?
4. When did you graduate from medical school?
5. What is your specialty?
6. Where is your primary practice located?
7. What kind of institution do you practice in?
8. Is your institution a community-base hospital for cancer care?
9. How many physicians are in your practice setting including you?
10. Are there any female physicians in your practice setting?
11. Are there any medical oncologists in your practice setting?
12. Are there any breast cancer specialized nurses in your practice setting?
13. Are there any cancer-specialized pharmacists in your practice setting?
14. Is there a genetic counseling clinic in your practice setting?
15. In a typical week, how many breast cancer surgeries are performed in your practice setting?
16. In a typical week, how many breast cancer patients under 40 years of age do you see?
17. Do you have a spouse/partner?
18. Do you have children?
19. Do you have relatives or close friends who passed away leaving behind minor children?

fertility preservation, the item was not included in our analysis. Participants were considered to be positive toward fertility preservation if the sum of scores was higher than 3. The sum of scores for statements from D-1 through D-5 was calculated and the respondents with higher total score were considered as physicians with a “positive attitude” towards fertility preservation.

5. Individual and institutional background

The items included physicians’ gender, age, religious background, length of professional career, and specialty. We also asked for a description of the practicing institution: the number of breast surgeries, the number of young breast cancer patients, presence of female colleagues in the team, the presence of one or more medical oncologist(s), breast cancer certified clinical nurse specialist (CNS), and board-certified pharmacists in the institution.

Procedures

The study was carried out according to the National Guideline for Epidemiological Studies. The names of study participants and the institutions of breast oncologists were obtained from the JBCS website. After confirmation of each physician’s affiliation, anonymous paper surveys were sent out to all 843 breast oncologists by mail with a return

postage-paid envelope. The survey was sent out on 28 May 2010 and the mailed surveys postmarked by 31 July were included in the analysis. The consent from the participants was waived because of the anonymity of the survey. No honorarium was offered for completing the survey.

Data analysis

All analyses were conducted using IBM SPSS statistics version 18. Accuracy of knowledge about fertility was scored on the basis of four questions (A-1, 2, 3, 4, Table 1) concerning the standard knowledge about chemotherapy and the effect of chemotherapy on fertility. Respondents with appropriate knowledge were considered “accurate”. Four questions (D-1, 2, 3, 5, Table 1) concerning the perspective and opinion about the fertility preservation were asked and scored as attitude score. Respondents were divided into “positive attitude group” and “negative attitude group” depending on the attitude score. Chi-square test was applied for correlation analysis between physician knowledge, attitude, and background. Physicians’ background demographics, knowledge, and attitude regarding fertility issues were associated with physicians’ practice behavior regarding fertility issues. Odds ratios (OR) and their 95% confidence interval (CI) were estimated to compare physician background factors, knowledge, and attitude with physician practice pattern, using simple and multivariable logistic regression models. All p values are two sided, and the statistical significance level was set at $p < 0.05$. No adjustments for multiple comparisons were considered because of the exploratory nature of this study.

Results

Response rate

The response rate was calculated as the number of breast oncologists completing the survey ($n = 434$) divided by the initial sample size minus undeliverable ($843 - 8 = 835$): this yielded a 52% response rate. This is higher than the previous survey on fertility preservation referral targeting oncology specialists in the USA [4].

Demographic and characteristics of responding breast oncologists

The background of respondents is shown in Table 2. A total of 16.6% of the respondents were female. More than 95% of the respondents were experienced physicians reflecting the requirement of basic board certification in general medicine, surgery, radiation oncology, or pathology in order to obtain JBCS Breast Oncologists

certification. The majority was surgeons. Less than half responded that they have medical oncologists in their institutions. About 70% were the institutions in which they operated on less than five breast cancer patients per week (less than approximately 200 cases per year).

Association between knowledge, attitude, and physician background

Two hundred and seventy-nine (64%) respondents were considered to have accurate knowledge. Accuracy of knowledge about fertility was correlated with the number of young breast cancer patients treated ($p = 0.006$), presence of children of the physician ($p = 0.01$), age of the physician ($p = 0.019$), and the presence of female colleagues ($p = 0.019$).

The existence of a spouse/partner ($p = 0.011$), age ($p = 0.032$), and gender ($p = 0.023$) of the physician were the factors significantly correlated with a positive attitude toward fertility considerations of breast cancer patients. Physicians who have a spouse/partner, physicians who are younger than 50 years, and female physicians had more positive attitudes toward fertility issues for breast cancer patients.

Practice of fertility issues among breast oncologists

A total of 83% of the participants responded that they were positive in discussing fertility issues with young breast cancer patients.

Twenty-one percent responded that patients voluntarily bring up fertility issues in the clinic. Physicians who treat two or more young patients per week perceived that patients voluntarily express their concern in the clinic compared to physicians who treat fewer (OR 1.84, 95% CI 1.13–3.00, $p = 0.008$). Physicians who treat two or more young patients per week (OR 1.30, 95% CI 1.05–2.45, $p = 0.023$), who have board-certified nurse colleagues (OR 1.55, 1.19–2.03, $p < 0.001$) and have more than six breast surgeries per week (OR 1.20, 1.02–1.41, $p = 0.014$) responded that they perceived that patients talk to co-medical staff about their concerns about fertility. A total of 24% of the respondents consulted reproductive specialists when they encountered fertility problems in their patients and 42% referred patients to reproductive specialists when patients expressed concerns regarding fertility.

The association between physicians’ behavior related to fertility issues and their knowledge, attitude, and background demographics are shown in Table 3. Fair knowledge had the strongest impact on physicians’ positive behavior towards discussing fertility issue with patients. Positive attitude, presence of breast cancer-specialized CNS, young age, and female gender were also significant

Table 2 Demographic background of the responding physicians

	<i>n</i>	%
Total	434	100
Gender		
Female	72	16.6
Male	357	82.3
Unknown	5	1.2
Age		
20–29	1	0.2
30–39	52	12.0
40–49	183	42.2
50–59	148	34.1
60–69	41	9.4
70–	4	0.9
Unknown	5	1.2
Religion		
Buddhist	144	33.2
Christian	9	2.1
No special religion	276	63.5
Others	5	1.2
Year graduated from medical school		
–1994	347	80.0
1995–2000	76	17.5
2001–2005	6	1.4
Unknown	5	1.2
Specialty		
Surgery	412	94.9
Medical oncology	6	1.4
Radiation oncology	9	2.1
Gynecology	1	0.2
Others	6	1.4
Type of affiliation		
Cancer center	40	9.2
General hospital	190	43.8
University hospital	122	28.1
Private clinic	74	17.1
Unknown	8	1.8
Number of physicians		
1–3	164	37.8
4–7	137	31.8
8–	125	28.8
Unknown	8	1.8
Female physician colleague		
Present	276	63.6
Absent	150	34.6
Unknown	8	1.8
Medical oncologist		
Present	172	39.6
Absent	255	58.8
Unknown	7	1.6

Table 2 continued

	<i>n</i>	%
Breast cancer specialized nurse		
Present	202	46.5
Absent	225	51.8
Unknown	7	1.6
Board-certified pharmacists		
Present	227	52.3
Absent	196	45.2
Unknown	11	2.5
Number of breast surgeries (per week)		
0–5	310	71.4
5–10	85	19.5
11–15	14	3.2
16–20	3	0.7
20–	14	3.2
Unknown	8	1.8
Number of patients aged <40 (per week)		
0–1	122	28.1
2–4	202	46.5
5–	103	23.7
Partner/spouse		
Present	401	92.4
Absent	25	5.8
Unknown	8	1.8
Children		
Present	351	80.9
Absent	64	14.7
Unknown	19	4.4

factors associated with positivity towards the discussion. Female oncologists and medical oncologists were more likely to take into account patients' social backgrounds such as history of childbirth, presence of a spouse/partner, and patients' economic status when discussing fertility issues.

Physicians with a positive attitude, physicians younger than 50 years, and female physicians were more likely to discuss fertility issues with patients with poorer prognoses. Positive attitude was the strongest factor related to consultation and referral to reproductive specialists.

Barriers for discussion with patients

High risk of disease recurrence (51%), lack of reproductive specialists or infertility clinic for referral (45%), and time constraints in the clinic (45%) were regarded as major barriers for discussing fertility issues. When only physicians who were negative in discussing fertility issues ($n = 69$) were analyzed, high risk of recurrence (57%), no signal of interest in fertility from patients (49%), and lack

Table 3 Factors associated with fertility-related practice behavior

	I discuss the impact of cancer treatment on future fertility with my patients				I do not feel comfortable discussing fertility issues with my patients				I take into account the history of childbirth when I discuss fertility issues with my patients			
	<i>p</i>	OR	95% CI		<i>p</i>	OR	95% CI		<i>p</i>	OR	95% CI	
			Min	Max			Min	Max			Min	Max
Knowledge												
Fair	0.000	1.717	1.321	2.231	0.063				0.799			
Not fair		1.000										
Attitude												
Conservative	0.012	1.000			0.180				0.697			
Aggressive		1.542	1.145	2.079								
Gender												
Female	0.005	1.166	1.080	1.258	0.807				0.022	1.130	1.041	1.227
Male		1.000								1.000		
Age												
<50	0.000	1.584	1.280	1.959	0.203				0.625			
>50		1.000										
Specialty												
Surgery	1.000				0.625				0.756			
Others												
Affiliation												
University hospital/cancer center	0.032	1.235	1.047	1.457	0.147				0.900			
General hospital/private hospital		1.000										
Female physician colleague												
Present	0.079				1.000				1.000			
Absent												
Medical oncologist colleague												
Present	0.432				0.366				0.043	1.190	1.003	1.141
Absent												
Breast cancer-specialized nurse												
Present	0.606				0.480				0.327			
Absent												
Board-certified cancer pharmacist												
Present	0.001	1.510	1.220	1.868	0.721				0.324			
Absent		1.000										
Number of breast surgeries per week												
1–5	0.884				0.692				0.495			
6–												
Number of young patients per week												
0–1	0.474				0.113				0.500			
2–												
Partner/spouse												
Present	0.281				0.008	1.000			0.193			
Absent						1.158	0.989	1.355				
Children												
Present	0.074				0.088				0.740			
Absent												

Table 3 continued

	I take into account whether she has a spouse/partner when I discuss fertility issues with my patients				I take into account economical status of the patient when I discuss fertility issues with my patients				I discuss fertility issues with breast cancer patients with high risk of recurrence			
	<i>p</i>	OR	95% CI		<i>p</i>	OR	95% CI		<i>p</i>	OR	95% CI	
			Min	Max			Min	Max			Min	Max
Knowledge												
Fair	0.839				0.609				0.910			
Not fair												
Attitude												
Conservative	0.601				0.694				0.001	1.000		
Aggressive										1.640	1.250	2.150
Gender												
Female	0.033	1.089	1.002	1.185	0.622				0.047	1.089	1.000	1.185
Male										1.000		
Age												
<50	0.326				0.267				0.003	1.391	1.131	1.712
>50												
Specialty												
Surgery	0.225				0.343				0.273			
Others												
Affiliation												
University hospital/cancer center	0.364				1.000				0.219			
General hospital/private hospital												
Female physician colleague												
Present	0.412				0.194				0.649			
Absent												
Medical oncologist colleague												
Present	0.022	1.206	1.032	1.408	0.043	1.261	0.996	1.596	1.000			
Absent		1.000				1.000						
Breast cancer specialized nurse												
Present	0.434				1.000				0.588			
Absent												
Board-certified cancer pharmacist												
Present	0.694				0.136				0.745			
Absent												
Number of breast surgeries per week												
1–5	0.125				0.262				0.903			
6–												
Number of young patients per week												
0–1	0.746				0.273				0.810			
2–												
Partner/spouse												
Present	0.299				0.192				1.000			
Absent												
Children												
Present	0.183				1.000				0.025	1.116	1.029	1.211
Absent										1.000		

Table 3 continued

	I ask co-medical staff if a patient has an interest in fertility			I provide my patients with educational material about fertility preservation			I use LHRH analogue to preserve fertility					
	<i>p</i>	OR	95% CI		<i>p</i>	OR	95% CI		<i>p</i>	OR	95% CI	
			Min	Max			Min	Max			Min	Max
Knowledge												
Fair	0.242			0.125				0.653				
Not fair												
Attitude												
Conservative	0.895			0.100				0.248				
Aggressive												
Gender												
Female	0.133			0.047	1.183	0.973	1.440	0.399				
Male												
Age												
<50	0.262			0.416				0.914				
>50												
Specialty												
Surgery	0.105			0.066				0.057				
Others												
Affiliation												
University hospital/cancer center	0.795			0.046	1.000			0.656				
General hospital/private hospital					1.671	0.959	2.911					
Female physician colleague												
Present	0.793			0.026	1.919	1.014	3.632	0.259				
Absent					1.000							
Medical oncologist colleague												
Present	0.443			0.407				0.381				
Absent												
Breast cancer-specialized nurse												
Present	0.316			0.871				0.516				
Absent												
Board-certified cancer pharmacist												
Present	0.900			0.325				0.663				
Absent												
Number of breast surgeries per week												
1–5	1.000			0.273				0.402				
6–												
Number of young patients per week												
0–1	0.583			0.721				1.000				
2–												
Partner/spouse												
Present	0.192			1.000				0.828				
Absent												
Children												
Present	0.614			1.000				0.156				
Absent												

Table 3 continued

	I consult a reproductive specialist with questions about fertility issues in my patients				I refer patients who have questions about fertility to reproductive specialists			
	<i>p</i>	OR	95% CI		<i>p</i>	OR	95% CI	
			Min	Max			Min	Max
Knowledge								
Fair	0.442				0.162			
Not fair								
Attitude								
Conservative	0.032	1.000			0.003	1.656	1.183	2.319
Aggressive		1.599	1.014	2.798		1.000		
Gender								
Female	0.039	1.121	0.995	1.277	0.001	1.176	1.062	1.302
Male		1.000				1.000		
Age								
<50	0.264				0.004	1.424	1.110	1.828
>50						1.000		
Specialty								
Surgery	1.000				0.795			
Others								
Affiliation								
University hospital/cancer center	0.007	1.349	1.067	1.706	0.012	1.243	1.047	1.474
General hospital/private hospital						1.000		
Female physician colleague								
Present	0.051	1.467	0.995	2.164	0.123			
Absent		1.000						
Medical oncologist colleague								
Present	0.103				0.042	1.212	1.011	1.453
Absent						1.000		
Breast cancer-specialized nurse								
Present	0.710				1.000			
Absent								
Board-certified cancer pharmacist								
Present	0.803				0.138			
Absent								
Number of breast surgeries per week								
1–5	0.785				1.000			
6–								
Number of young patients per week								
0–1	0.270				0.813			
2–								
Partner/spouse								
Present	0.807				0.670			
Absent								
Children								
Present	0.197				0.209			
Absent								

of reproductive specialists or infertility clinic for referral (38%) were the major causes for them not to discuss fertility with patients.

Discussion

This study describes the attitude of the main providers of breast cancer treatment in Japan towards fertility issues in young breast cancer patients. The high response rate to our survey in a relatively short time indicates the interest of breast oncologists in fertility issues. More than 80% of the participants responded that they had a positive attitude when discussing fertility issues in the clinic, but this result may be biased by the respondents' interest in fertility issues. The recent awareness of fertility issues among Japanese breast oncologists may be related to the publication of the ASCO guideline in 2006 and the inclusion of fertility-related contents in JBCS patient guideline 2009 [2, 9]. Indeed, the JBCS treatment guideline, the standard textbook for board certification of Breast Oncologists, updated its contents to cover fertility-related issues in July 2010 [10].

The physicians with a positive attitude and working in institutions with medical oncologists and/or female colleagues had a higher likelihood of consultation or referral to reproductive specialists. The likelihood of referring to reproductive specialists was slightly higher in female physicians, which was consistent with the results of the survey in the USA [4]. These results indicate that participation of female healthcare providers in the team and a multidisciplinary working environment might enhance physicians' awareness of and behavior toward fertility-related issues. Because knowledge and attitude seem to be influenced by gender, personal experience, and the working environment of the physicians, we think that outreach with educational materials and systematic learning opportunities for healthcare providers would be helpful in expanding knowledge and performance regarding fertility issues in young breast cancer patients.

High risk of disease recurrence was considered the greatest barrier for physicians, similar to the results of other studies [5, 6]. In our previous study, patients' with higher risk of disease recurrence did not voluntarily express their concerns regarding fertility when compared to patients of lower risk of disease recurrence [3]. Both patients and physicians may refrain from discussing future fertility when the estimation of prognosis of the cancer is poor. Although early referral to reproductive specialists might increase the patients' likelihood of receiving reproductive intervention and improve the fertility outcome [11, 12], fertility preservation techniques such as embryo preservation and oocyte preservation connote ethical issues especially in patients with poor prognosis [13]. Ethical and

psychosocial support is necessary in the shared decision-making process among patients, families, and physicians.

A lack of reproductive specialists or infertility clinic for referral is a real problem. A survey in the USA showed that many breast cancer clinicians reported that they do not have knowledge of or resources for fertility preservation [8, 14]. Interdisciplinary communication between reproductive specialists and oncologists is necessary.

Early case-control studies suggest that pregnancy after primary treatment of breast cancer does not have a negative impact on cancer prognosis, although "healthy mother" bias might exist [15]. Because prognostication of breast cancer has become individualized using genetic biomarkers [16, 17], further investigations to clarify the impact of pregnancy after primary treatment on an individual basis is needed so that patients can personalize their decision-making regarding both cancer treatment and fertility.

In conclusion, Japanese breast oncologists were in general positive in discussing fertility issues with young breast cancer patients. Female and younger physicians as well as physicians working in a multidisciplinary environment had more positive attitudes and behavior towards fertility preservation. The development of multidisciplinary and interdisciplinary programs is necessary to meet the fertility needs of breast cancer patients.

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Paclitaxel-induced peripheral neuropathy in patients receiving adjuvant chemotherapy for breast cancer

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Abstract

Background The long-term outcomes and risk factors of paclitaxel-induced peripheral neuropathy (PIPNe) have not yet been fully elucidated.

Methods We identified 219 breast cancer patients who received paclitaxel as adjuvant chemotherapy between 2002 and 2009. We retrospectively analyzed the incidence, time to onset, duration, and risk factors for PIPNe by chart review.

Results Of the 219 patients, 212 developed PIPNe (97%) during a median follow-up time of 57 months (range 5.3–95.5). Median time to PIPNe onset was 21 days (range 11–101) for the entire patient population: 35 days (range 14–77) for weekly administration and 21 days (range 11–101) for tri-weekly administration. PIPNe caused termination of paclitaxel treatment in 7 patients (4%). Median duration of PIPNe was 727 days (range 14–2621 days). PIPNe persisted in 64 and 41% of patients at 1 and 3 years after initiating paclitaxel, respectively. Age ≥ 60 years and severity of PIPNe were significantly associated with PIPNe duration.

Conclusions PIPNe persists longer in older patients and in those who experience severe neuropathy. Further studies to identify the risk factors for PIPNe are warranted.

Keywords Breast cancer · Paclitaxel · Peripheral neuropathy

Introduction

Paclitaxel (PTX) is a key component of many therapeutic regimens in both early-stage and metastatic breast cancer [1–4]. PTX, a microtubule-stabilizing agent, binds to microtubules and abolishes their dynamic behavior, leading to inhibition of cell proliferation [5]. The agent is known to cause peripheral neurotoxicity (PN), which may result in discontinuation of treatment and poor quality of life.

The incidence of PTX-induced PN (PIPNe) is known to depend on several factors, including dosages per cycle, treatment schedule, duration of infusion, cumulative dosage, and co-morbidity such as diabetes [6–11]. Although the clinical response of tumors to PTX is an important factor in selecting a chemotherapy regimen, it is also prudent to evaluate the risk of developing PN associated with each regimen, especially for patients already at high risk for neuropathy. The risk of sensory neuropathy is proportional to the dose of PTX administered. Grade 3 or 4 sensory neurotoxicity occurs in 20–35% of patients receiving 250 mg/m² every 3 weeks compared to 5–12% using doses ≤ 200 mg/m² every 3 weeks [12]. The weekly schedule is associated with higher neurotoxicity than the tri-weekly schedule. In a previous study, grade 3 neuropathy occurred significantly more often with the weekly regimen than with the tri-weekly regimen (24 vs. 12%) [13]. In another study, which compared weekly versus

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tri-weekly PTX dosages, it was reported that grade 2, 3, or 4 neuropathy occurred more frequently with weekly than with tri-weekly PTX administration (27 vs. 20%, respectively) [14].

The time to onset of PIPN was previously determined in a phase III trial of patients with metastatic breast cancer treated with PTX (175 mg/m^2) every 3 weeks; the mean total dose at the onset of grade 2 neurotoxicity was 715 mg/m^2 [15]. However, there are limited data available describing the outcome of PIPN and risk factors of severe PN. We therefore conducted a retrospective study to determine the duration of PIPN and to identify potential factors predicting severe or persistent PN.

Patients and methods

Data collection

This study included breast cancer patients treated with PTX as adjuvant chemotherapy at the National Cancer Center Hospital between 2002 and 2009. All patients met the following criteria: female gender; age >18 years; recipients of lumpectomy or mastectomy; and presentation of more than one axillary lymph node metastasis, as determined pathologically. The following patients were excluded from this study: those previously treated with PTX, those who presented with severe neuropathy before initiating PTX treatment, and those who discontinued PTX treatment after only 1 cycle for any reason.

We performed chart reviews for all patients to obtain the following information: age; gender; stage; hormonal status; human epidermal growth factor receptor-2 (HER2) status; previous surgical procedures (lumpectomy or mastectomy); adjuvant chemotherapy; adjuvant radiotherapy; PTX administration schedule; date of the first documentation of PIPN; maximum grade of PIPN; date of disappearance of PIPN symptoms. This study was approved by the local institutional review board.

Treatment schedule

Chemotherapy consisted of anthracycline followed by PTX regimens as generally recommended for high-risk breast cancer patients, according to the St. Gallen risk criteria at our division [16, 17]. However, therapeutic options could vary based on the physician's discretion. Patients received either 80 mg/m^2 of PTX on days 1, 8, and 15 of each 21-day interval for 4 cycles, following anthracycline plus cyclophosphamide (AC) (weekly administration schedule), or 175 mg/m^2 of PTX on day 1 of each 21-day interval for 4 cycles, following AC (tri-weekly administration schedule).

Grading of PIPN

Patients were evaluated during and after chemotherapy by medical oncologists. We graded PIPN retrospectively according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 [18]. Grade 1 PIPN had paresthesias including tingling, but not interfering with function, while grade 2 had sensory alterations or paresthesias interfering with function but not interfering with activities of daily living (ADL). Grade 3 had sensory alterations or paresthesias interfering with ADL. Patients were determined to have PIPN if their score for sensory neuropathy was grade 1 or higher. The severity of pain was not evaluated in this study because of insufficient data.

Statistical analysis

The time to onset of PIPN was defined as the time from the date of PTX administration to the date of the first documentation of PIPN. The duration of PIPN was defined as the time from the date of first documentation of PIPN to the date of disappearance of the PIPN symptoms described. The time to onset and duration of PIPN were estimated by the Kaplan–Meier method. We used multivariate Cox regression analysis to identify the variables associated with the time to onset and duration of PIPN. Furthermore, to identify the risk factors for PIPN above grade 2, we applied multivariate logistic regression analysis. A 2-sided $P < 0.05$ was considered statistically significant. All analyses were performed by SAS software, version 9.2 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

Of the 227 patients initially identified, 2 were excluded due to severe neuropathy induced by combination chemotherapy with AC before being treated with PTX. Several patients discontinued systemic therapy before completion of 1 cycle due to the following adverse events: severe liver dysfunction (grade 3) ($n = 3$), acute renal failure (grade 3) ($n = 1$), allergic reaction (grade 3) ($n = 1$), and interstitial pneumonitis (grade 3) ($n = 1$). Finally, a total of 219 patients were included; 212 patients (97%) developed PIPN which was characterized by numbness and tingling, while 7 had no PIPN symptoms. The maximum severity of PIPN reached in each of the 212 patients was as follows: grade 1, 159 patients (75%); grade 2, 45 patients (21%); and grade 3, 9 patients (4%). Two patients needed dose modifications due to PIPN above grade 2. No patients postponed or skipped the scheduled PTX due to PIPN.

Baseline characteristics of the population are listed in Table 1. The median age of patients was 53 years (range 22–70). Eighteen patients had diabetes mellitus without neuropathy complications at baseline. Disease-free survival and overall survival were evaluated with a median follow-up time of 57.1 months (range 5.3–95.5). A total of 25 patients received weekly PTX: 23 following AC and 2 without AC. The remaining 194 patients received tri-weekly PTX: 182 following AC and 12 without AC. The mean dose intensity was 58 mg/week (range 16–80). Treatment cessation was deemed necessary in 9 patients (4%); reasons for cessation were PIPN (8 patients, 3 with

grade 1, 1 with grade 2, and 5 with grade 3) and myelosuppression (1 patient).

PIP development time

The median time taken for the total patient group to develop PIPN was 21 days (range 11–101) (Fig. 1). With weekly administration of PTX, the median time taken to develop PIPN was also 21 days (range 11–101); the median time with tri-weekly administration was 35 days (range 14–77).

Cumulative dose

The mean cumulative dose at the onset of grade 1 or higher PIPN was 175 mg/m² for patients treated with PTX every 3 weeks and 320 mg/m² for weekly PTX patients.

Diabetes mellitus

Of 18 diabetic patients, all had PIPN and 3 had maximum grade 3 PIPN. Median time to PIPN onset was 21 days (range 20–21), and median duration of PIPN was 287 days (range 70–503). In patients without diabetes, median time to PIPN was 21 days (range 20–21), and median duration of PIPN was 231 days (range 190–271).

Risk factors correlated with PIPN

Multivariate analysis using a logistic regression model after stepwise selection revealed no significant correlations between time to PIPN onset and maximum PIPN severity (Table 2), while there were significant correlations between duration of PIPN and age (>60 years old) ($P = 0.027$) and between duration of PIPN and maximum PIPN severity ($P = 0.015$) (Table 3). Moreover, we could not identify

Table 1 Patient characteristics

Variables	triPTX (N = 188)	wPTX (N = 24)	All (N = 212)
Age			
Median (range)	53 (22–70)	52 (32–68)	53 (22–70)
<60 (%)	141 (75.0)	17 (70.8)	158 (74.5)
≥60 (%)	47 (25.0)	7 (29.2)	54 (25.5)
Sex (%)			
Female	187 (99.5)	24 (100.0)	211 (99.5)
Male	1 (0.5)	0 (0.0)	1 (0.5)
Lymph (%)			
<4	118 (62.8)	12 (50.0)	130 (61.3)
≥4	70 (37.2)	12 (50.0)	82 (38.7)
Tumor size (%)			
<5 cm	153 (81.4)	18 (75.0)	171 (80.7)
≥5 cm	35 (18.6)	6 (25.0)	41 (19.3)
Surgery (%)			
Mastectomy	114 (60.3)	16 (66.7)	130 (61.3)
Lumpectomy	73 (39.2)	8 (33.3)	81 (38.2)
Excisional biopsy	1 (0.5)	0 (0.0)	1 (0.5)
Systemic therapy (%)			
Chemo	56 (29.8)	8 (33.3)	64 (30.2)
Chemo + endocrine	132 (70.2)	16 (66.7)	148 (69.8)
Radiation (%)			
No	69 (36.7)	8 (33.3)	77 (36.3)
Yes	119 (63.3)	16 (66.7)	135 (63.7)
Hormone (%)			
Negative	48 (25.5)	5 (20.8)	53 (25.0)
Positive	140 (74.5)	19 (79.2)	160 (75.0)
HER2 (%)			
Negative	156 (83.0)	16 (66.7)	172 (81.1)
Positive	32 (17.0)	8 (33.3)	40 (18.9)
Diabetes mellitus (%)			
No	171 (91.0)	23 (95.8)	194 (91.5)
Yes	17 (9.0)	1 (4.2)	18 (8.5)

triPTX tri-weekly paclitaxel, wPTX weekly paclitaxel, chemo chemotherapy

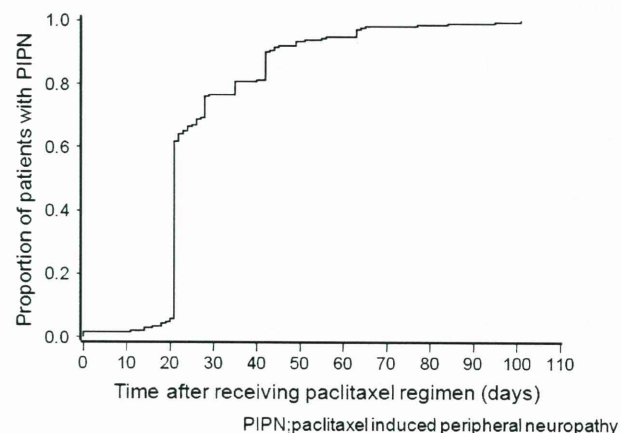


Fig. 1 Time taken for the total patient group to develop paclitaxel-induced peripheral neuropathy

Table 2 Multivariate analysis for factors associated with time to PIPN

Variables	HR	95% CI	<i>P</i> value	
Regimen				
triPTX	1			
wPTX	0.66	0.43	1.03	0.070
Age				
<60				
≥60	0.99	0.72	1.37	0.960
Lymph				
<4				
≥4	1.20	0.82	1.77	0.341
Tumor size (cm)				
<5				
≥5	0.98	0.68	1.42	0.917
Radiation				
No				
Yes	0.78	0.51	1.20	0.259
Surgery				
Mastectomy				
Lumpectomy	1.08	0.75	1.56	0.666
Endocrine				
No				
Yes	0.87	0.65	1.18	0.366
Grade				
1				
2 or 3	1.35	0.97	1.87	0.073
Diabetes mellitus				
No				
Yes	1.34	0.81	2.21	0.260

PIP_N paclitaxel-induced peripheral neurotoxicity, *triPTX* tri-weekly paclitaxel, *wPTX* weekly paclitaxel, *HR* hazard ratio, *CI* confidence interval

any correlation with grade 2/3 PIPN (Table 4). Based on the results of multivariate analyses, there were no significant associations between diabetes mellitus and time to PIPN onset ($P = 0.260$) or duration of PIPN ($P = 0.345$) or grade 2/3 PIPN ($P = 0.229$).

Duration of PIPN

The median duration of PIPN was 727 days for the total patient group (range 14–2621) (Fig. 2). With weekly administration, the median duration was not reached (range 14–1089); the median duration for patients with tri-weekly administration was 651 days (range 23–2621). One year after initiating PTX treatment, PIPN (all grades included) persisted in 64% of patients; 3 years after treatment initiation, this number had dropped to 41%.

Table 3 Multivariate analysis for factors associated with duration of PIPN

Variables	HR	95% CI	<i>P</i> value	
Regimen				
triPTX	1			
wPTX	0.48	0.19	1.21	0.119
Age				
<60				
≥60	0.55	0.32	0.94	0.027
Lymph				
<4				
≥4	0.86	0.46	1.59	0.621
Tumor size (cm)				
<5				
≥5	1.03	0.59	1.77	0.927
Radiation				
No				
Yes	1.05	0.52	2.12	0.900
Surgery				
Mastectomy				
Lumpectomy	0.67	0.36	1.26	0.213
Endocrine				
No				
Yes	1.10	0.70	1.73	0.668
Grade				
1				
2 or 3	0.53	0.32	0.88	0.015
Diabetes mellitus				
No				
Yes	0.66	0.28	1.56	0.345

PIP_N paclitaxel-induced peripheral neurotoxicity, *triPTX* tri-weekly paclitaxel, *wPTX* weekly paclitaxel, *HR* hazard ratio, *CI* confidence interval

Discussion

This is the first published report to our knowledge that investigates the time to onset and duration of PIPN among breast cancer patients and explores potential risk factors related to severe and/or persistent PIPN. The data from this study confirm that most patients (97%) developed PIPN with a severity of at least grade 1. Peripheral neuropathy persisted in 64% of patients at 1 year and 41% at 3 years after the first administration of PTX. Approximately half of the patients who received PTX and developed PN experienced recovery from PN within 9 months after cessation of PTX treatment. We found correlations between the maximum PIPN severity and both the time to onset of PIPN and the duration of PIPN. In addition, we observed that PN lasted significantly longer in patients >60 years of age.

Table 4 Multivariate analysis for factors associated with grade 2 or 3 PIPN

Variables	Odds ratio	95% CI	<i>P</i> value
Regimen			
triPTX	0.57	0.18–1.83	0.345
wPTX			
Age			
<60	1.65	0.81–3.36	0.171
≥60			
Lymph			
<4	0.98	0.40–2.41	0.968
≥4			
Tumor size (cm)			
<5	0.47	0.18–1.24	0.125
≥5			
Radiation			
No	0.98	0.35–2.77	0.975
Yes			
Surgery			
Mastectomy	0.73	0.29–1.82	0.499
Lumpectomy			
Endocrine			
No	0.72	0.36–1.45	0.360
Yes			
Diabetes mellitus			
No	2.05	0.69–6.09	0.197
Yes			
Dose intensity			
<58	1.00	0.50–2.01	1.000
≥58			
Cumulative dose			
<700	0.31	0.08–1.13	0.077
≥700	0.57	0.18–1.83	0.345

PIP_N paclitaxel-induced peripheral neurotoxicity, *triPTX* tri-weekly paclitaxel, *wPTX* weekly paclitaxel, *CI* confidence interval

Previous studies have reported that the incidence of PIPN is related to several risk factors, including treatment schedule, doses per course, patient age, diabetes mellitus, and cumulative dose [6–11]. We found no association between the severity of PIPN and the PTX administration schedule including single dose, dose intensity, diabetes mellitus, or interval of administration. In our study, the mean cumulative dose at the onset of grade 1 or higher PN was 175 mg/m² for patients treated with PTX every 3 weeks and 320 mg/m² for weekly PTX patients. In contrast to an earlier study [14], our clinical outcomes indicated that tri-weekly administration of PTX was associated with more severe PIPN than weekly administration. However, this result may be attributed to frequent hospital

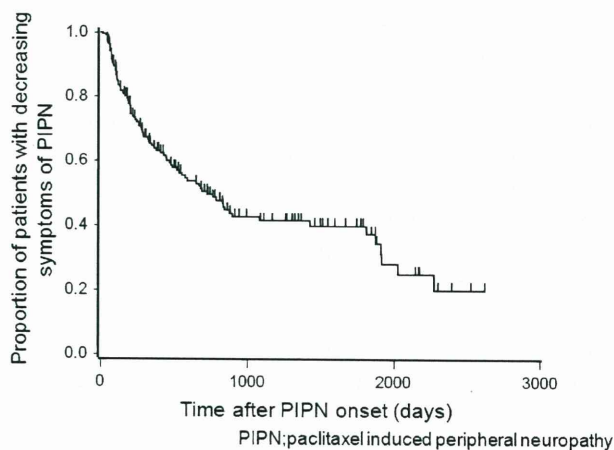


Fig. 2 Time to resolving PIPN from the time of developing paclitaxel-induced peripheral neuropathy

visits and/or the relatively small number of patients treated by weekly PTX.

Previous reports suggest there are several risk factors for PIPN, including concurrent administration of cisplatin [19] and various genetic predispositions for neuropathy, such as *Wlds* (slow Wallerian degeneration gene) and *CYP3A* genotype [20, 21], but we did not examine any of those risk factors in this study.

Axonal microtubules are composed largely of β -tubulin. Neurotoxicity is caused by disruption of the microtubule structure, impairing axoplasmic transport and leading to dying-back neuropathy [22]. The most widely accepted mechanism of taxane neurotoxicity is a dying-back process that starts from distal nerve endings and progresses to affect Schwann cells, neuron bodies, or axons, resulting in transport changes that disturb cytoplasmic flow in the affected neurons [23]. Another possible cause of PIPN is that sensory nerves may be particularly vulnerable to the inhibition of tubulin assembly, as sensory nerves have long axons. However, motor neurons and C-neurons are not as sensitive to taxanes as are sensory nerves, despite the fact that these neurons are as long as sensory nerves. Some reports suggest that induction of *Cax2 δ -1* expression by PTX in the spinal root may be important, but further investigation is necessary to understand the mechanisms of PIPN [24].

There are no medications that prevent or relieve PIPN. Likewise, there are no laboratory tests that can predict the severity of PN. Management of PIPN is now based on early detection during chemotherapy to prevent its progression to grade 3 or 4. Clinical assessment, including a physical examination, is currently the most reliable method of assessing PIPN because we lack more reliable objective methods, and the symptoms of PIPN, such as numbness, sensory pain, fatigue, and weakness, are complicated [12, 25]. If grade 2 PN is diagnosed, it may be prudent to

withhold PTX until PN improves to at least grade 1; PTX administration can then be resumed at a reduced dose.

There were several limitations to our study. We used physician-based assessments, which relies on patients' report and examiners' interpretation and could have resulted in underestimation and under-reporting of the frequency and severity of PN [26]. In addition, physicians were more prone to quit following symptoms periodically once patients recovered from maximum PIPN. In fact, there were many censored cases in this study (Fig. 2). Therefore, features of PIPN such as location, presence of accompanying symptoms, and triggers for increase or decrease in severity were unclear. This study was retrospective, with censored data; the neurotoxicity corresponding to each grade of PIPN was unclear. In fact, time to onset of PIPN was faster for grades 2 and 3 than grade 1. In order to properly evaluate the correlation between severity and duration of PIPN, we will need further studies to determine whether or not the duration of PIPN is longer when the maximum severity increases from grade 1 to grade 2.

In conclusion, we analyzed the incidence and duration of PIPN and identified correlations between these and several risk factors. We found that the median time to onset of PIPN was 21 days, and the median duration of PIPN was 727 days. Patient age and PIPN severity were the independent risk factors significantly associated with longer PIPN duration. Urgent needs currently include identification of specific risk factors for PIPN, establishment of subjective methods for evaluating PIPN, and development of effective strategies for prevention and treatment of PIPN. To meet these ends, further investigation of the biological mechanisms leading to PIPN is warranted.

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Conflict of interest The authors have declared no conflicts of interest.

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● 原 著 ●

乳癌薬物治療に伴う妊孕性への影響に関する情報提供の実態調査

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Survey on Oncologists-Provided Information on Treatment-Related Infertility to Breast Cancer Patients: Akiko Kubo*¹, Keiichi Koido*¹, Mari Sawada*¹, Yasuaki Ryushima*¹, Chikako Shimizu*², Tomoyasu Kato*³, Masashi Ando*², Takayuki Kinoshita*², Koji Murakoshi*¹, Nobuaki Yokote*¹, Yasuhiro Fujiwara*² and Hiroshi Yamamoto*¹ (*¹Dept. of Pharmacy, *²Dept. of Breast and Medical Oncology, and *³Dept. of Gynecology, National Cancer Center Hospital)

Summary

Purpose: Treatment-related infertility is an important issue facing breast cancer survivors of childbearing age. A previous study at the National Cancer Center Hospital between 2000 and 2004 analyzed 136 postoperative breast cancer patients under 40 years old, and found that only 7% of them had been provided with information on fertility-related issues by their treating physicians. However, the way in which information is shared may have changed, given the recent publication of national and international guidelines on fertility issues in cancer patients, and we hypothesized that there will be an increase in the percentage of cases in which information about fertility-related issues is provided. Methods: We retrospectively analyzed patients 40 years old or younger who underwent surgery for primary breast cancer in this hospital between 2007 and 2009. We assessed patients' and oncologists' backgrounds, pathological stage, treatment plans, and whether or not oncologists provided explanations regarding fertility-related issues. Results: One hundred cases were analyzed. Five percent, 15%, and 80% of patients were <30, 30-35, and >35 years old, respectively. Sixty-one percent of patients had partners, while 29% had prior deliveries. Information on fertility-related issues was provided to 56% of patients. Significant factors influencing whether information was provided were patients' reproductive history (odds ratio (OR): 5.717, 95% confidence interval (CI): 1.752-18.66, p=0.004) and recommended treatment (OR: 24.22, CI: 3.150-186.2, p=0.017). By contrast, oncologists' background (specialty, gender, and duration of career as a physician) was not significant. The frequency with which treatment plans were changed did not correlate statistically with the provision of information on fertility-related issues. Conclusions: Information on treatment-related infertility is now provided much more frequently than in the past. We should encourage both patients and medical professionals to increase their awareness about this important issue. Key words: Breast cancer, Chemotherapy, Infertility (Receive May 13, 2011/Accepted Jul. 6, 2011)

要旨 背景: 薬物治療に関連した不妊は育児希望を有する乳癌患者にとって重要な問題である。国立がん研究センター中央病院(以下、当院)における2000~2004年を対象期間とした調査では、40歳以下の乳癌患者に術前・術後薬物療法が妊孕性に及ぼす影響が伝えられていたのは7%だった。今回、われわれは2007~2009年における情報提供の実態調査を行った。方法: 2007~2009年に当院で手術を受けた40歳以下の女性乳癌患者を対象とした。診療録から、妊孕性に関する医師からの情報提供の有無、患者および担当医師の社会的背景、治療レジメンを後方視的に調査した。結果: 対象患者は100名。年齢[<30歳/30~35歳/35歳≤]=[5/15/80]、病理病期[0/I/II/III/IV]=[21/23/43/12/1]、パートナー[あり/なし]=[61/39]、出産歴[あり/なし]=[29/71]であった。情報提供[あり/なし]=[56/44]であった。情報提供の有無に影響する因子は、患者側の要因として出産歴(odds ratio (OR): 5.717, 95% CI: 1.752-18.66, p=0.004)や推奨される治療レジメン(OR: 24.22, 95% CI: 3.150-186.2, p=0.017)と関連がみられ、年齢やパートナーの有無は関連がみられなかった。また、医師側の背景因子(診療科、性別、医師経験年数)との関連はみられなかった。さらに、化学療法を含む治療方針からの変更割合は、情報提供の有無で差はみられなかった。結語: 2007~2009年においても、情報提供率は約60%にとどまり、癌治療に伴う妊孕性への影響について、医療者・患者双方の意識をさらに高める必要がある。

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はじめに

近年、診断技術や治療技術の進歩に伴い、がん患者の予後が改善されてきたことで、治療後のQOL向上が懸念されるようになった。その一つとして、治療に関連した不妊がある¹⁾。

乳癌の化学療法では卵巣機能障害が比較的高率に起きる。特に cyclophosphamide (CPA) は、治療後に永続的な無月経を惹起しやすい代表的な抗がん剤として報告されている²⁾。乳癌は生殖年齢における罹患率が高く、挙児希望を有する乳癌患者にとって妊孕性への影響は重要な問題である。

2006年の米国臨床腫瘍学会 (ASCO) の勧告では、医師は生殖能力を有する患者を治療する場合には、治療開始前に治療に伴う妊孕性の影響について十分に説明し、生殖医療の専門医への紹介を行うべきであるとしている。

しかし、国立がん研究センター中央病院 (以下、当院) において2000～2004年を対象期間とした調査では、40歳以下の早期乳癌患者の術後補助療法を決定する際に、医師から患者に対し治療による妊孕性への影響について、積極的に説明が行われた頻度は7%にとどまった³⁾。

本邦においても、2006年の日本乳癌学会の患者向けガイドラインに抗がん剤治療に伴う妊孕性への影響が明記される⁴⁾など、患者を取り巻く情報環境に変化が現れはじめています。そこで今回、われわれは2006年以降における情報提供の実施状況の実態を明らかにするために調査・検討を行った。

I. 対象と方法

1. 対象患者

2007年1月～2009年10月までの期間に当院乳癌外科で乳房切除術を施行した、手術時年齢が40歳以下の早期乳癌女性患者を対象とした。

2. 調査方法および調査項目

調査は診療録を用いて後方視的に行った。調査項目は、妊孕性に関する情報提供の有無、対象患者における年齢、病理病期 (pStage)、パートナーの有無、出産歴の有無、医師から推奨された補助療法および実施された補助療法とした。なお、情報提供の有無はインフォームド・コンセント時の診療録に、不妊・早発閉経などの記載があった場合に、「情報提供あり」と判断した。

妊孕性に関する情報提供頻度の変化を調べるため、岡田らが報告した2000～2004年を対象期間とした症例をA群、今回調査を行った2007～2009年を対象期間とした症例をB群として比較を行った。患者背景における年

齢の分類は、A群の調査に準じて行った。

情報提供の有無を決定する可能性のある背景因子として、患者側の要因 (年齢、パートナーの有無、出産歴の有無、推奨された治療) および各対象患者における担当医師側の要因 (診療科、性別および医師経験年数) の影響を検討した。

3. 統計学的処理

2群間の比較には χ^2 検定を用いた。薬物治療に伴う妊孕性への影響に関する情報提供の有無にかかわる背景因子については、多重ロジスティック回帰分析により検討した。解析ソフトは、SPSS 15.0 J for Windowsを使用した。

II. 結果

1. 患者背景

B群の対象患者は100名であった。年齢中央値は37.5歳、年齢 [<30 歳/ $30\sim35$ 歳/ 35 歳 \leq] = [5/15/80]、パートナー [あり/なし] = [61/39]、出産歴 [あり/なし] = [29/71] であった。情報提供 [あり/なし] = [56/44] であった。また、術後に遠隔転移が発覚した患者 (pStage IV) が1名認められた。

Table 1に両群の患者背景を示す。両群を比較すると、年齢層に差が認められ ($p < 0.0001$)、B群では35歳以上の患者が増加した。また、「出産歴あり」はA群が52.9%、B群が29%と有意に減少した ($p = 0.0002$)。なお、pStage、パートナーの有無では両群間に有意な差は認めなかった。

2. 妊孕性に関する情報提供の実施状況

担当医から患者に対し薬物治療に伴う妊孕性への影響に関する情報提供の実施頻度を示す (Fig. 1)。なお、B群で他の医療職種 (看護師) から情報提供が行われていた症例が1例あったが、担当医からの説明の有無は不明であったため、「情報提供なし」と分類した。「情報提供あり」はA群が7%、B群が56%で8倍に増加した ($p < 0.0001$)。

3. 情報提供の有無に関連する背景因子

B群における情報提供の有無に関連する背景因子について解析した結果を示す (Table 2, 3)。患者側の要因として、出産歴なし [odds ratio (OR): 5.717, 95% CI: 1.752-18.66] と推奨補助療法がホルモン治療 (OR: 9.436, 95% CI: 1.219-73.05)、化学療法 (OR: 24.22, 95% CI: 3.150-186.2) が有意なリスク因子であることが明らかとなった。患者の年齢やパートナーの有無は関連性がみられなかった (Table 2)。また、担当医師側の要因として、診療科、性別、医師経験年数はいずれも情報提供の有無に影響しなかった (Table 3)。これらの結果から、情報提供