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Practice management for elderly patients with breast cancer; Findings from a survey by the Japan Breast Cancer Study Group

Masataka Sawaki[1], Kenji Tamura[2], Akihiko Shimomura[2], Yumiko Taki[1], Fumio Nagashima[3], and Hiroji Iwata[1]

[1]*Department of Breast Oncology, Aichi Cancer Center Hospital, Nagoya, Japan*
[2]*Department of Breast and Medical Oncology, National Cancer Center Hospital, Tokyo, Japan*
[3]*Department of Medical Oncology, Kyorin University School of Medicine, Tokyo, Japan*

ABSTRACT

Information on patterns of clinical care for elderly breast cancer patients is lacking. The aims of this study are two-fold, firstly, to clarify daily practice treatments for elderly breast cancer patients in Japan, and secondly, to plan a prospective clinical trial to address unresolved clinical questions. We investigated practice care of elderly breast cancer patients in 38 institutions of the Japan Clinical Oncology Group (JCOG). Questionnaires asked: (1) definition of "elderly" for each treatment, (2) clinical standard anti-HER2 therapy in each age-group, (3) recommended docetaxel dose in each age-group, (4) considerations for future clinical trials, and (5) other information about geriatric oncology concerning breast cancer. The upper age-limit for surgery and irradiation therapy was generally 80 years, while many physicians considered anti-cytotoxic adjuvant therapy unsuitable for patients >70–75 years. For HER2-positive metastatic breast cancer, 82% of physicians recommended docetaxel (DTX) plus trastuzumab plus pertuzumab (DTP) as standard care for patients aged 65–70, although 54% of physicians avoided DTP for those aged 71–75 as first-line standard preference. Most physicians recommended 75 mg/m^2 DTX for both 65–70 (63%) and 70–75 (52%) age-groups, but not for those over 75. Many physicians (73%) recommended 60 mg/m^2 DTX first. Most (97%) agree that the vulnerability of each elderly patient in a clinical trial should be assessed by comprehensive geriatric assessment. This is the first questionnaire study of care patterns for elderly breast cancer patients. Physicians considered different drug regimens and dosages according to patients' fragility.

Keywords: breast cancer, elderly, practice management, survey

INTRODUCTION

Breast cancer has been the most prevalent cancer in women in Japan for the last 20 years, and morbidity has been increasing for over 40 years.[1)] According to the Surveillance, Epidemiology,

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Corresponding author: Masataka Sawaki, MD, PhD
Department of Breast Oncology, Aichi Cancer Center Hospital, 1-1 Kanokoden, Chikusa-Ku, Nagoya 464-8681, Japan
Phone: +81-52-762-6111, Fax: +81-52-764-2963, Email: m-sawaki@aichi-cc.jp

and End Results (SEER) program of the National Cancer Institute, the median age at diagnosis of breast cancer is 62 years, 42.8% of cases occur in women aged 65 and over, and 19.4% of new diagnoses are in women aged over 75.[2] Another study found that, in Japan, there were two distinct peaks observed in the population-adjusted age distribution of breast cancer patients: one in patients in their late 40s and the second in those in their early 60s.[1] In a practice setting for elderly breast cancer patients, many treatment options are necessary because of their comorbidity, low organ function, and poor performance status. This frailty of elderly patients sometimes means that not enough elderly patients receive treatment and also causes a high rate of adverse events, resulting in a low rate of positive outcomes even though patients have received standard treatment. Moreover, there are few data to suggest guidelines for standard treatments of elderly breast cancer patients,[3] because they have potentially been underrepresented in clinical trials.[4] Women in Japan have the highest life expectancy in the world (World Health Statistics 2016), therefore it is particularly important to establish standard care for elderly breast cancer patients especially in Japan. The aims of this study are two-fold, firstly, to clarify daily practice treatments for elderly breast cancer patients in Japan, and secondly, to plan a prospective clinical trial to address unresolved clinical questions.

METHODS

Study Design and Study Population

The study population consisted of attendees at the 38 participating institutions of the Japan Breast Cancer Study Group, which is a subgroup of the Japan Clinical Oncology Group (JCOG). It is the official cooperative group for the treatment of breast cancer. Each institution was selected based on strict criteria including their expertise in breast cancer treatment. Study participants were asked to fill in a single form, which consisted of a study-specific questionnaire comprising 11 questions, some requiring information from the institution's elderly patients' database. The questionnaires were sent to each institution using a mailing list in February 2015. Physicians in each institution answered these questions and returned the responses by e-mail. The respondents were instructed to give answers concerning the institutional policy, not the personal opinion. In cases with no response a reminder was sent by e-mail. All answers were collected and analyzed by M.S. and Y.T (Aichi Cancer Center).

RESULTS

Conduct of the Survey and Completion Rates

Between February and May 2015, a total of 33 respondents participated in this study. The return rate of the questionnaire was 86.8% (33/38 institutes), and physicians answered the 11 questions individually. The results were presented at the Japan Breast Cancer Study Group meeting on 17 October 2015, and discussed among the attending members and the JCOG Data Center. The questionnaire was originally written in Japanese, and the questions are listed below.

Q1. What is the recommended upper age limit to perform surgery for breast cancer?

The most frequent upper age limit was 80 years (Fig. 1). Twenty-six percent of the doctors also answered that age is not an important factor when choosing a therapeutic approach. The most important factors to take into account when deciding on treatment for breast surgery were given as follows: performance status (PS) (n = 4), comorbidity (n = 3), general condition (n = 3), activities of daily living (ADL) (n = 1), preference (n = 1).

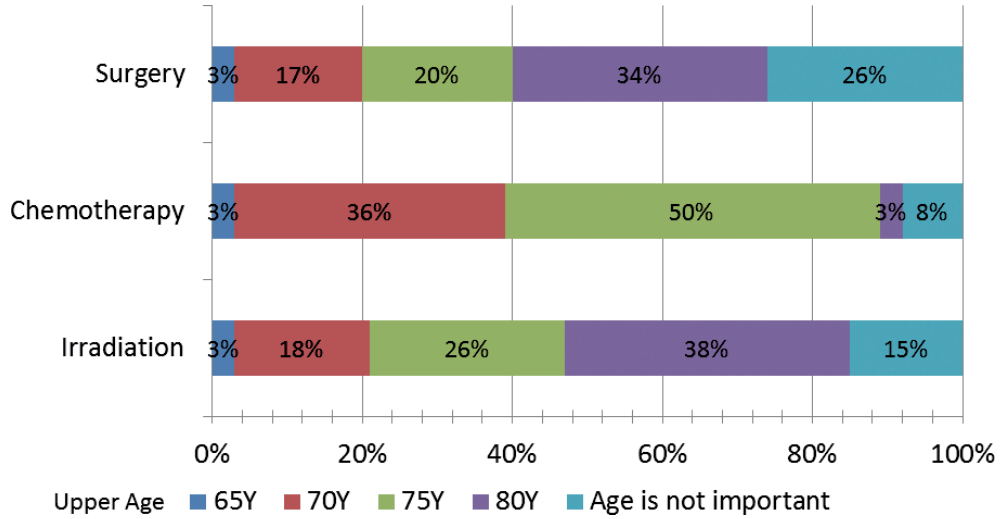

Fig. 1 Recommended upper age limit for the use of each treatment modality in elderly breast cancer patients

Q2. What is the recommended upper age limit to administer chemotherapy for breast cancer?

Seventy-five years of age was the most frequent upper age limit given (Fig. 1). The most important factors when deciding on the use of anti-cytotoxic agents for breast cancer were listed as follows, PS (n = 1), comorbidity (n = 2), preference (n = 1), organ function (n = 1).

Q3. What is the recommended upper age to administer irradiation therapy for breast cancer?

Eighty years old was the most frequent upper age limit given (Fig. 1). The most important factors to take into account when deciding whether to apply irradiation therapy for breast cancer were as follows; PS (n = 3), general condition (n = 1), hospital transportation (n = 1), the organs to be irradiated (n = 1).

Q4. How many patients underwent breast surgery or received chemotherapy in your institution between January and December 2014 according to each subtype?

The number of patients is shown in Tables 1 and 2. In patients older than 70 years, 11.9% of those with ER-positive breast cancer received chemotherapy. On the other hand, in patients with HER2-positive or triple-negative disease, 39.3% and 48.0%, respectively, received chemotherapy. In patients over 65 years of age, a greater proportion of the patients received chemotherapy.

Table 1 Patients older than 65 years of age who underwent chemotherapy according to intrinsic subtype

Subtype	Number	Patients who underwent chemotherapy (%)
ER+ (>1%), HER2–	2,094	364 (17.4%)
ER+ (>1%), HER2+	209	115 (55.0%)
ER–, HER2+	261	133 (51.0%)
ER–, HER2–	351	166 (47.3%)

Table 2 Patients older than 70 years of age who underwent chemotherapy according to intrinsic subtype

Subtype	Number	Patients who underwent chemotherapy (%)
ER+ (>1%), HER2–	1,348	161 (11.9%)
ER+ (>1%), HER2+	125	60 (48.0%)
ER–, HER2+	159	65 (40.9%)
ER–, HER2–	219	86 (39.3%)

Q5. What is the recommended regimen for first-line treatment of HER2-positive metastatic breast cancer in patients from 65 to 70 years of age?

As the first preference, 82% of physicians recommended docetaxel (DTX) + trastuzumab+ pertuzumab treatment (Fig. 2A). As the second preference, 39% of physicians recommended paclitaxel (PTX) + trastuzumab + pertuzumab treatment.

Q6. What is the recommended regimen for first-line HER2-positive metastatic breast cancer in patients from 71 to 75 years of age?

As the first preference, 46% of physicians recommended DTX + trastuzumab+ pertuzumab treatment (Fig. 2B). As the second preference, 23% of physicians recommended T-DM1 or DTX + trastuzumab + pertuzumab treatment.

Q7. What is the recommended regimen for first-line HER2-positive metastatic breast cancer in patients from 76 to 80 years of age?

As the first preference, 23% of physicians recommended DTX + trastuzumab+ pertuzumab treatment (Fig. 2C). As the second preference, 20% of physicians recommended single taxane treatment.

Q8. What is the recommended regimen for HER2-positive metastatic breast cancer in patients over 80 years old?

As the first preference, 26% of physicians recommended single taxane treatment (Fig. 2D). As the second preference, 26% of physicians also recommended single taxane treatment.

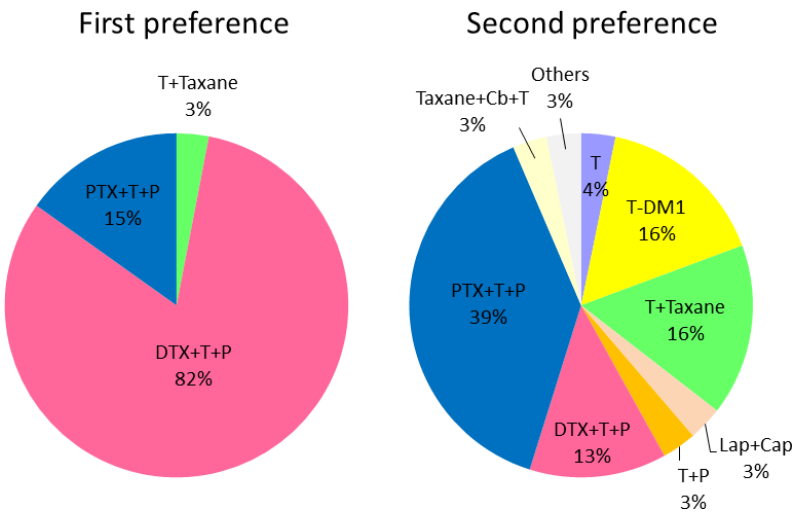

Fig. 2A The recommended regimen for HER2-positive metastatic breast cancer in patients aged 65 to 70 years Abbreviations: DTX, Docetaxel; PTX, Paclitaxel; T, Trastuzumab; P, Pertuzumab; Lap, Lapatinib; Cb, Carboplatin

Q9. What dose of docetaxel (DTX) do you recommend in elderly patients with metastatic breast cancer if you use combination chemotherapy of DTX + trastuzumab + pertuzumab according to age? (Assuming PS0, adequate organ function.)

In those aged 65–70 years old, the majority of physicians (63%) recommended doses of 75

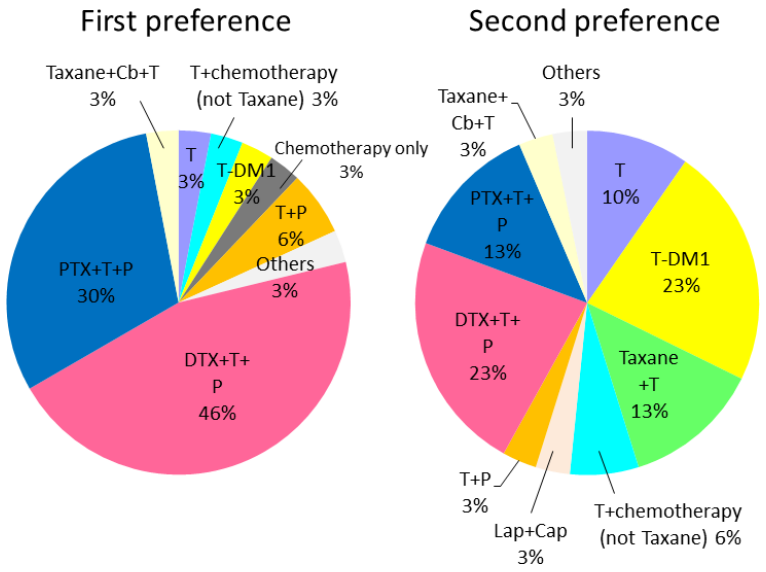

Fig. 2B The recommended regimen for HER2-positive metastatic breast cancer in patients aged 71 to 75 years Abbreviations: DTX, Docetaxel; PTX, Paclitaxel; T, Trastuzumab; P, Pertuzumab; Lap,Lapatinib; Cap, Capecitabine; T-DM1, Trastuzumab-emtansine

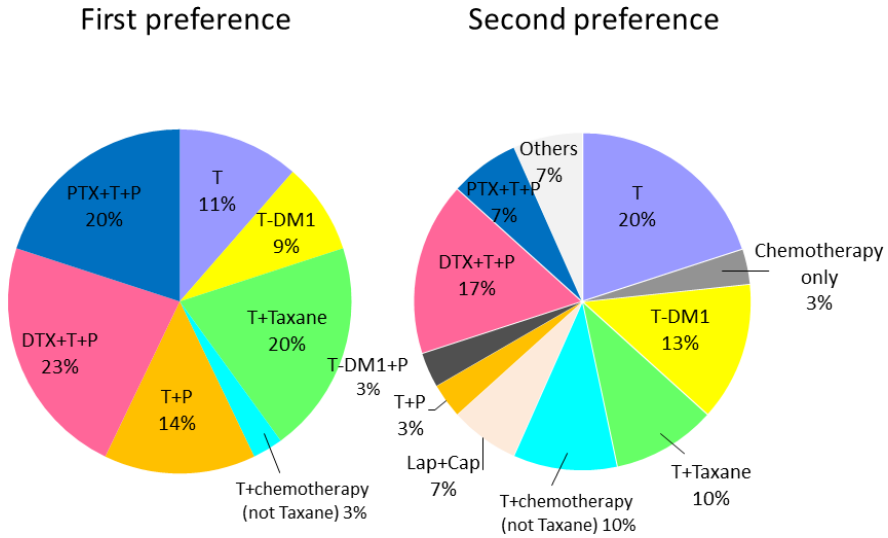

Fig. 2C The recommended regimen for HER2-positive metastatic breast cancer in patients aged 76 to 80 years Abbreviations: DTX, Docetaxel; PTX, Paclitaxel; T, Trastuzumab; P, Pertuzumab; Lap, Lapatinib; Cap, Capecitabine; T-DM1, Trastuzumab-emtansine

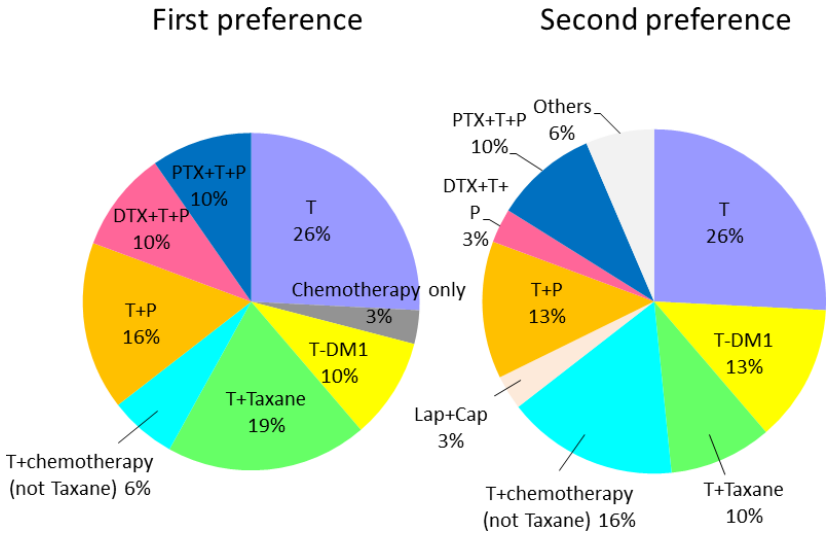

Fig. 2D The recommended regimen for HER2-positive metastatic breast cancer in patients over 80 years of age Abbreviations: DTX, Docetaxel; PTX, Paclitaxel; T, Trastuzumab; P, Pertuzumab; Lap, Lapatinib; Cap, Capecitabine; T-DM1, Trastuzumab-emtansine

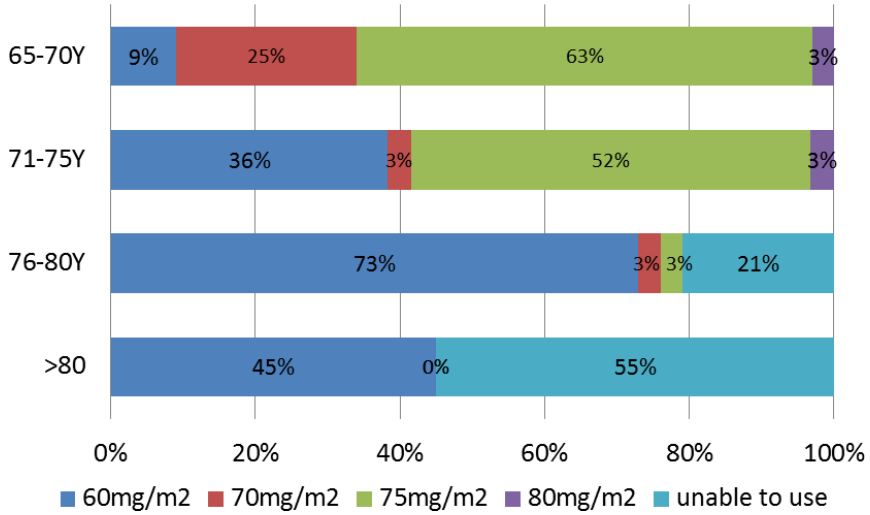

Fig. 3 Recommended doses of docetaxel in elderly patients with metastatic breast cancer when combined with trastuzumab and pertuzumab (in patients with good performance status and adequate organ function)

mg/m^2, which is the standard dose, while in patients aged 71–75, 52% of physicians also recommended 75 mg/m^2. On the other hand, in those aged 76–80 years, the majority of physicians (73%) recommended a dose of 60 mg/m^2, but in patients over 80 years, 55% of physicians thought it could not be used adequately (Fig. 3).

Q10. What is the upper age limit for the use of T-DM1?

In total, 73% of physicians thought it was suitable for use in patients up to 80 years of age,

while 27% thought it was suitable for use in patients over 80 years.

Q11. Do you agree with the need for a clinical trial using comprehensive geriatric assessment (CGA) to make decisions regarding treatment in elderly breast cancer patients?

In total, 97% of physicians agreed with the proposal.

DISCUSSION

This is the first report of a questionnaire study in Japan analyzing the patterns of care carried out by a well constituted large cooperative group and specifically concerning elderly breast cancer patients. In patients with breast cancer, age over 70 is commonly regarded as the threshold above which they require specialized elderly breast cancer treatment. For elderly patients, individual breast examination depends on medical indication, the patient's wishes, and presumed life expectancy,[5] but patients should not receive less effective treatment simply because of age alone. However, it can be difficult to make a treatment decision. Consequently, we first reviewed daily practice in elderly patients from member institutions of the JCOG to clarify practice treatments for elderly breast cancer patients, because in the practice setting there are many treatment options but few data to suggest standard treatments in elderly breast cancer patients. The Japan Breast Cancer Study Group is the official cooperative group; most of the members are also key opinion leaders in the field of breast cancer treatment in Japan. The opinion of the group is considered to be one of consensus in all Japan.

In elderly patients, surgery for breast cancer may be as safe as in those of a younger age and is recommended if life expectancy is more than 5 years.[6] As a result of this question, 80 years old was the most frequently-cited upper age for surgery. Most physicians think that surgical treatment of breast cancer is feasible for these patients. With regard to irradiation therapy, most physicians also believe it is feasible for elderly patients, as it is effective regardless of age.[7] On the other hand, with regard to treatment with anti-cytotoxic agents, many physicians believe that this treatment is too unpleasant for patients over 70 or 75 years of age to bear. For breast cancer, in particular as adjuvant chemotherapy, treatment with anti-cytotoxic agents is not always standard therapy in elderly patients based on the analysis of data from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) because of limited data.[8] Elderly patients have potentially been underrepresented in clinical trials. If chemotherapy is administered, most physicians believed that 75 years of age was the most appropriate upper age limit in most cases, and the most important factors affecting application of anti-cytotoxic agents are comorbidity, preference and organ function. Life expectancy of breast cancer patients should be taken into account when deciding on appropriate treatments.

When making a treatment decision in elderly patients, CGA is an important tool, which uses a multidisciplinary approach, although its style has not been standardized. CGA is a process for designing a cancer treatment plan based on evaluation of the vulnerability of elderly patients from various perspectives. The components of CGA include comorbidity, physical function, cognitive function, psychological status, social support care system, nutrition, and medication. CGA may predict adverse events of chemotherapy,[9] and finds geriatric problems, as a result of which geriatric support and adequate treatment can be provided.[10] Several kinds of tools for CGA have been used to identify patients with a geriatric risk and to evaluate their likely prognosis. Recently, two tools: G8 and a Flemish version of the Triage Risk Screening Tool (fTRST), were compared to identify patients with geriatric risks and to assess their prognosis with regard to functional decline.[11] These tools are both simple and useful in an elderly population with cancer. In this questionnaire, in total, 97% of physicians agreed that CGA is used appropriately

in a clinical trial. A prospective investigation of the CGA and tools such as G8 and fTRST in elderly Japanese breast cancer patients is required to respond to these problems.

We used the questionnaire to focus on anti-HER-2 therapy in an elderly population and on the key decisions regarding treatment to address unresolved clinical questions and to know the number of patients because we are planning a new clinical trial mainly targeted HER-2 positive metastatic breast cancer. For HER2-positive metastatic breast cancer in patients aged between 65 and 70 years of age, 82% of physicians recommended treatment with DTX plus trastuzumab plus pertuzumab, which is also standard therapy.[12] As the second preference, 39% of physicians recommended PTX plus trastuzumab plus pertuzumab, which is an alternative chemotherapy.[13] On the other hand, in patients aged from 70 to 75 years, only 46% of physicians recommended DTX plus trastuzumab plus pertuzumab treatment as a first preference. As the second preference, 23% of physicians recommended treatment with T-DM1 or DTX plus trastuzumab plus pertuzumab.

Pertuzumab is an anti-HER2 humanized monoclonal antibody that inhibits receptor dimerization, which has a mechanism of action that is complementary to that of trastuzumab. Then, they provide a more comprehensive blockade of HER2 signaling and result in greater antitumor activity, when given together, than either agent alone. In the pivotal study using pertuzumab, the combination of pertuzumab plus trastuzumab plus docetaxel significantly prolonged progression-free survival without increasing cardiac toxic effects as compared with placebo plus trastuzumab plus docetaxel when used as first-line treatment for HER2-positive metastatic breast cancer.[14] However there is little information available with respect to elderly patients in this or other trials.[14-16] In the CLEOPATRA trial, subset analysis was performed in 127 patients aged over 65 years.[17] Patients in both age-groups showed better progression-free survival with treatment in the pertuzumab arm (<65 years: HR: 0.65; 95% CI 0.53–0.80; ≥65 years: HR: 0.52; 95% CI 0.31–0.86). As for adverse events in the trial, diarrhea, fatigue, asthenia, decreased appetite, vomiting, and dysgeusia were reported more frequently in patients 65 years of age or older compared with younger patients. In addition, the median number of treatment cycles in elderly patients was six, in contrast to younger patients in whom it was eight. Dose reduction of docetaxel was more often necessary in the elderly patients resulting in lower relative dose intensity. In the NeoSphere trial, which aims to inhibit ligand-dependent signaling between HER2 and HER3 in a neoadjuvant setting, no information about efficacy or safety of treatment in elderly patients was available, although the upper age limit for inclusion was 80 years.[15] T-DM1 is an antibody–drug conjugate incorporating the HER2-targeted antitumor properties of trastuzumab with the cytotoxic activity of the microtubule-inhibitory agent DM1. In a pivotal T-DM1 study, T-DM1 significantly prolonged progression-free and overall survival compared to lapatinib plus capecitabine, with less toxicity in patients with HER-2-positive metastatic breast cancer previously treated with trastuzumab and taxane.[18] In the MARIANNE trial, T-DM1 showed no inferiority against trastuzumab plus either docetaxel or paclitaxel and also resulted in the fewest adverse events, indicating that monotherapy with T-DM1 would be acceptable for elderly patients and could be one of the alternative regimens instead of trastuzumab/taxane or trastuzumab/pertuzumab/taxane. In this questionnaire, many physicians thought that T-DM1 would be acceptable in patients over 75 years of age and even in those over 80 years old, because of its lower toxicity. In this questionnaire, a total of 73% of physicians thought it could be used in patients under 80 years regardless of the lack of data. DTX is a standard regimen for adjuvant treatment and metastatic breast cancer, although the standard dose varies widely, ranging from 60 to 100 mg/m^2. In the metastatic setting 75–100 mg/m^2 is the most popular and best evidence-based dose, because this dose has been used in many pivotal trials.[12] In the CLEOPATRA trial, febrile neutropenia, neutropenia, diarrhea, edema and appetite loss were more frequent in the Asian population than in the western population.[19] In other cancer types, for example, 60 mg/m^2 of docetaxel was

recommended in Japanese advanced non-small lung cancer patients,[20] suggesting there are ethnic differences in acceptability of docetaxel. A dose of 60 mg/m^2 of docetaxel was acceptable in the Japanese metastatic breast cancer population.[21,22] Especially in the elderly population, increased risk of febrile neutropenia caused by three-weekly docetaxel (16% in patients 65 years old or older compared with 0% in their younger counterparts) is not due to altered pharmacokinetics (PK) but to increased bone marrow sensitivity.[23] Therefore, 100 mg/m^2 is not recommended for elderly patients.[24] In this questionnaire, a dose of 75 mg/m^2 or 70 mg/m^2 was recommended in patients aged 65–70 years, while in those aged 70–75 years 52% of physicians also recommended 75 mg/m^2. However in the 75–80 age-group, a dose of 60 mg/m^2 was recommended, while in patients over 80 years, 55% of physicians thought its use was inappropriate. The elderly-specific side effect of each treatment strategy has been uncertain, and then we would make it clear in the clinical trial in the future.

As for patients with hormone responsive breast cancer, most of patients underwent hormone therapy without cytotoxic chemotherapy. Other new agents such as CDK4/6 inhibitor and mTOR inhibitor are important in metastatic setting, although its safety for elderly patients is uncertain. And also we have to consider its cost.

In conclusion, for elderly breast cancer patients, we should select treatment with the lowest toxicity but comparative survival benefit considering their life expectancy and quality of life. The opinion of experts in the field of breast cancer treatment provides valuable information to plan a future prospective trial in elderly breast cancer patients. Geriatric assessment tools are also helpful to address a potential weakness of studies in the heterogeneous general population and should be included in any prospective clinical trial. Further objective investigations of elderly breast cancer patients that include the use of geriatric assessment tools are warranted.

CONFLICTS OF INTEREST STATEMENT

The authors state that there is no conflict of interest.

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