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Clinical Trial Note

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Multi-institutional phase II study of ultra-hypofractionated whole-breast irradiation after breast-conserving surgery for breast cancer in Japan: Kyoto Radiation Oncology Study Group (UPBEAT study)

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Abstract

Purpose: The UK-FAST-Forward study showed that ultra-hypofractionated whole-breast irradiation (ultra-HF-WBI) involving five fractions of 26 Gy radiation over 1 week was not inferior to HF-WBI. However, it is not used in Japan due to safety concerns. In April 2022, we commenced a multi-institutional, single-arm, phase II trial. Our aim is to confirm the safety of ultra-HF-WBI after breast-conserving surgery (BCS) for breast cancer in Japanese women.
Method: We plan to enroll 98 patients from 13 institutions. The primary endpoint is the proportion of late adverse events of grades $\geq$2 within 3 years.
Discussion: We believe that this highly promising clinical study can positively impact the Japanese guidelines for breast cancer treatment. The results will help us decide whether or not ultra-HF-WBI can be used as a more convenient alternative to WBI.
Registration number and date: This trial was registered in the UMIN Clinical Trials Registry (UMIN000047080) on March 4, 2022.

Key words: breast cancer, phase II study, ultra-hypofractionated, whole-breast irradiation

Introduction

Breast cancer is the most common cancer in Japanese women; approximately 94 000 breast cancer patients were diagnosed in Japan in 2018 (1). Almost 80% of the newly diagnosed cases in Japan are in clinical stage I or II, and are recommended to undergo breast-conserving surgery (BCS) following whole-breast irradiation (WBI) for the entire breast according to the guidelines (2,3). Conventionally fractionated WBI (CF-WBI, 50 Gy in 25 fractions over 5 weeks) has been empirically and standardly performed in Japan as WBI after BCS. Recently, hypofractionated WBI (HF-WBI, 40 or 42.56 Gy over 3 weeks in 15 and 16 fractions, respectively), in which a larger per-fraction dose is administered in fewer fractions over a shorter period, has become a standard fractionated radiation therapy schedule for WBI after BCS, based on the results of randomized clinical trials (4,5) and the JCOG0906 study in Japan (6,7).

The UK-FAST-Forward study conducted a phase III randomized clinical trial to demonstrate the non-inferiority of ultra-HF-WBI (26 or 27 Gy in 5 fractions over 1 week) to HF-WBI (40 Gy in 15 fractions over 3 weeks). This study was published in April 2020 and reported that ultra-HF-WBI was non-inferior at 5 years in terms of local recurrence and provided lower acute and similar late normal tissue effect rates compared with HF-WBI (8). However, to the best of our knowledge, ultra-HF-WBI has not been used as WBI after BCS in Japan. Given the differences in body sizes between Western and Japanese women and the frequency of radiation-induced dermatitis and radiation pneumonitis, safety concerns about the use of ultra-HF-WBI in the Japanese population persist.

Therefore, we designed a multi-institutional, single-arm, phase II trial to confirm the safety of ultra-HF-WBI, compared with HF-WBI or CF-WBI, after BCS for breast cancer. The eligibility criteria in this study are different from those in the UK-FAST-Forward study. In this study, participants will be limited to patients who needed irradiation to the conserved breasts only and those who do not need boost irradiation to the tumor beds. This is because the treatment methods including the operative techniques, radiation fields and total doses need to be unified to ensure the safety of ultra-HF-WBI in a limited number of participants. Thus, patients who have undergone total mastectomy for breast cancer are not eligible. Only those who have undergone BCS are eligible. Patients whose pathologic diagnosis is invasive carcinoma or ductal carcinoma *in situ* are also eligible because their irradiation fields and doses are the same. On the other hand, patients whose surgical margins are positive, as well as relatively young patients that are under 40 years of age, who require boost irradiation, are not eligible.

The 13 hospitals in the Kyoto Radiation Oncology Study Group (KROSG) will participate in the trial. The study protocol was approved by the Research Ethics Committee of Kobe City Medical Center General Hospital on March 4, 2022 and was registered under the title 'Ultra-hyPofractionated BrEast radiotherapy After breast-conserving surgery for early-stage breasT cancer (UPBEAT study)'. Patient registration began in April 2022.

Protocol digest of UPBEAT study

Objectives

This single-arm phase II study aimed to confirm the safety of ultra-HF-WBI in Japanese women after BCS for breast cancer.

Study setting

This multi-institutional, single-arm phase II study will be conducted on behalf of the KROSG. Figure 1 shows the trial schema, including the eligibility criteria.

Endpoints

The primary endpoint is the proportion of adverse events of grade ≥ 2 occurring within 91 days to 3 years from the initiation of ultra-HF-WBI. The secondary endpoints are the proportions of acute adverse events of grades ≥2 and late adverse events of grades ≥2, overall

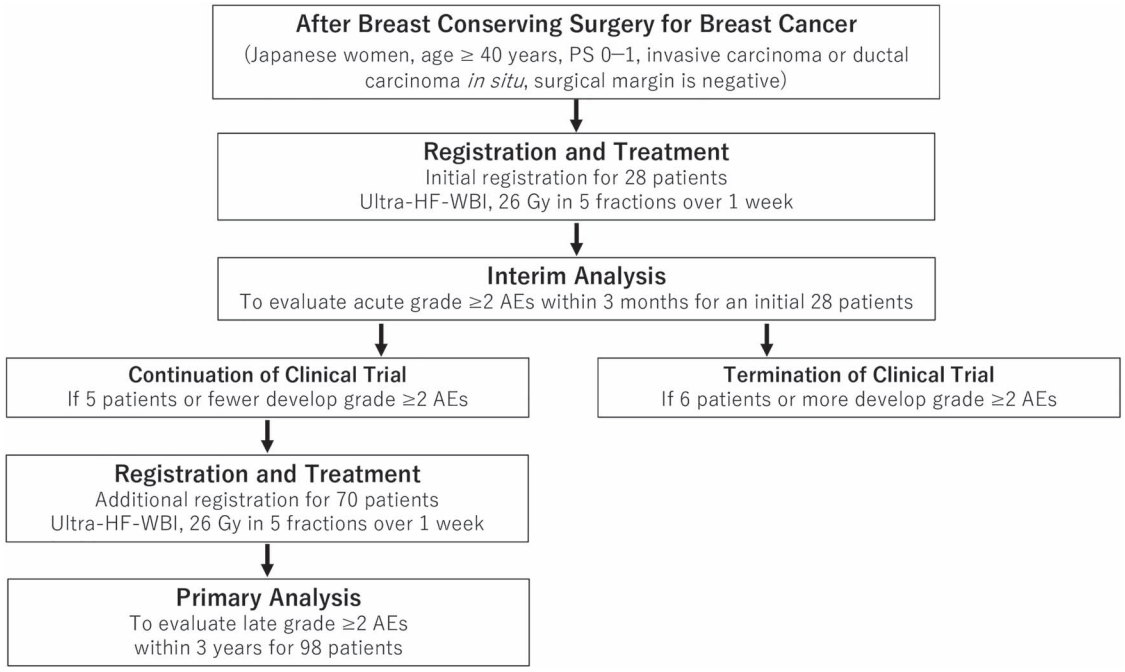

Figure 1. Schema of this study.

survival (OS), progression-free survival (PFS) and ipsilateral breast tumor relapse-free survival (IBRFS). The time until the occurrence of adverse events and all survival times start from the commencement of ultra-HF-WBI. An acute adverse event is defined as an adverse event that occurred within 90 days. A late adverse event is defined as an adverse event that occurred within 91 days to 5 years. Adverse events will be assessed using the Common Terminology Criteria for Adverse Events (version 5.0; US National Cancer Institute, Bethesda, MD). OS is defined as the time to death from any cause. PFS is defined as the time to recurrence or death from any cause. IBRFS is defined as the time to ipsilateral breast tumor relapse or death from any cause.

Eligibility criteria

Patients are required to fulfill the following eligibility criteria: no distant metastasis on any examination before surgery; having undergone BCS for breast cancer; pathological eligibility criteria including invasive carcinoma or ductal carcinoma *in situ*, pathological stage of Tis-3 N0-N1 and negative surgical margin; radiation therapy started within 70 days of surgery or 42 days from the last day of adjuvant chemotherapy; Japanese ethnicity and female gender; age of ≥40 years at the time of registration; Eastern Cooperative Oncology Group performance status of 0–1; no prior radiation therapy was administered to the chest except for radiation therapy to the contralateral breast; and written informed consent obtained in Japanese.

Exclusion criteria

Patients meeting any of the following conditions will be excluded: history of synchronous or metachronous (within 5 years) malignancies, except for carcinoma *in situ* or intramucosal carcinoma that is curable with local treatment; active infection requiring systemic therapy; fever with a body temperature higher than 38.0°C at the time of first registration; pregnant, possibly pregnant and breastfeeding females; psychiatric illnesses or symptoms affecting daily life; uncontrolled diabetes (e.g. HbA1c > 7%); interstitial pneumonia, pulmonary fibrosis or heavy pulmonary emphysema; systemic treatment with steroids; active collagen disease requiring immunosuppressive agents; heavy heart disease, heart failure or history of myocardial infarction or angina pectoris within 6 months before registration; and patients determined to be inappropriate for this study by physicians.

Treatment methods

Radiation therapy

Ultra-HF-WBI will be delivered to the whole breast at a daily dose of 5.2 Gy and up to a total of 26.0 Gy in five fractions over 5 days using 4–10 MV X-rays. Boost irradiation is not permitted in this case. A tumor bed boost will not be administered to patients over 40 years of age in most Japanese institutions if a sufficient surgical margin has been created (3,9). Deep inspiratory breath-hold during irradiation, which is a common technique for reducing the heart dose in left-sided breast radiation therapy, is recommended, but not essential. Radiation therapy treatment planning will follow the Japanese Society for Radiation Oncology Guidelines 2020 for radiotherapy treatment planning, except for daily dose and total fractions. The clinical target volume (CTV) will include the soft tissues of the whole breast, excluding the muscle and the underlying rib cage. A margin will be added to the CTV, taking into account set-up error, breast swelling and breathing, with a typical planning target volume (PTV) margin of 5 mm for all PTV volumes. The PTV for a dose-volume histogram (PTV_DVH) has been defined to evaluate the PTV dose. This structure will be cropped to 5 mm inside the skin and 5 mm from the lung surface. The organs at risk (OAR) are the ipsilateral lung and heart. The body, PTV_DVH and OAR dose constraints are presented in Table 1.

Systemic therapy

Systemic therapy will only be allowed in accordance with the Japanese Breast Cancer Society Clinical Practice Guidelines for the Systemic Treatment of Breast Cancer. Hormonal and anti-HER2 therapies will be allowed during ultra-HF-WBI, but chemotherapy will not be allowed. Supportive therapy, such as the use of topical medication to treat radiation dermatitis and painkillers to reduce skin pain, will be allowed.

Follow-up

All enrolled patients will be followed up for at least 5 years after the completion of treatment. After 3 years, an analysis of the primary endpoint will be conducted. Physical examination will be conducted within 2 weeks from the last day of ultra-HF-WBI, at 3 and 6 months, and every year after 5 years from the start of ultra-HF-WBI. Mammography will be performed annually for all patients.

Study design and statistical analysis

This single-arm trial was designed to confirm the safety of ultra-HF-WBI in terms of the proportion of adverse events of grades ≥2 within 3 years in Japanese women after BCS, compared with HF-WBI or CF-WBI. If the proportion of late adverse events of ultra-HF-WBI does not exceed that of HF-WBI or CF-WBI, we will conclude that ultra-HF-WBI is a more convenient option for patients because of its shorter treatment duration.

The required sample size is 90 patients with a one-sided alpha level of 10%, power of 80%, threshold value of 10% and expected value of 4.3%, which was determined based on the proportion of late adverse events of grade ≥ 2 within 3 years in the JCOG0906 study (6,7), using the exact test of a binomial proportion. The total sample size will be 98 to account for patients who will fail to follow up. Analyses will be performed for all treated patients. All statistical analyses will be conducted by the study coordinator at Kobe City Medical Center General Hospital and the KROSG.

Interim analysis and monitoring

An interim analysis will be conducted three months after the registration of 28 patients. The required sample size for the interim analysis is 25 patients with a one-sided alpha level of 10%, power of 80%, threshold value of 30% and expected value of 12.4%, which was determined based on the proportion of acute adverse events of grades ≥2 within 3 months in the JCOG0906 study (6,7), using the exact test of a binomial proportion. The total sample size in the interim analysis will be 28 to account for patients who will fail to follow-up. After 28 patient registers, patient registration will be paused for 3 months. After 3 months, acute adverse events of grades ≥2 will be evaluated. If acute adverse events of grades ≥2 are detected in 5 or fewer patients, we will conclude that the proportion of adverse events associated with the treatment in this protocol is more acceptable than those of HF-WBI and CF-WBI, and we will, thereafter, resume

Table 1. Dose constraints of targets and organs at risk

		Mandatory	Optimal
Target			
PTV_DVH	Lower limit	V90% ≥ 90%	V90% ≥ 95%
		V105% ≤ 7%	V105% ≤ 5%
	Upper limit	V107% ≤ 2%	
		Dmax ≤110%	
Organs at risk			
Body	Upper limit	Dmax ≤110%	
Ipsilateral lung	Upper limit	V30% ≤ 17%	V30% ≤ 15%
Heart	Upper limit	V25% ≤ 5%	
		V5% ≤ 25%	

Abbreviations: Dmax = maximum point dose to an organ or tumor target in radiotherapy cancer treatment. VX% = percentage of an organ or tumor target volume receiving at least X% of the prescription dose.

patient registration. However, if acute adverse events are detected in six or more patients, we will conclude that the proportion of adverse events associated with the treatment in this protocol is not acceptable. The study will be discontinued because ultra-HF-WBI is not a safe treatment for Japanese women.

In-house monitoring will be performed every year by the study coordinator at Kobe City Medical Center General Hospital and KROSG to evaluate the progress and improve the quality of the study.

Scheduled analyses

In this study, we have estimated a registration period of 2 years. After completing the registration of 98 patients, we will follow them up to evaluate their safety and effectiveness. The primary analysis will be conducted after 3 years. Two years later, the final analysis will be conducted. We assume that 1 year is required to analyse the data. The total research duration is expected to be 8 years.

Brief discussion, importance and possible impact of the study

The advantage of ultra-HF-WBI is that the total radiation treatment period is shortened from 3–5 weeks to 1 week. This reduces hospital visits and the financial and physical burden on patients. With fewer hospital visits, the risk of COVID-19 infection is lowered. International guidelines on radiation therapy for breast cancer during the COVID-19 pandemic recommend that ultra-HF-WBI should be delivered to patients requiring radiation therapy for node-negative tumors that do not require boost irradiation (10,11). After the COVID-19 pandemic, a decrease in the total radiation treatment period with the use of ultra-HF-WBI will also lead to a reduction in the burden of WBI on patients. This is an advantage, especially for patients who have to undergo mastectomy with WBI over 3–5 weeks, as they will be have the option of selecting BCS followed by ultra-HF-WBI as an alternative treatment plan.

In summary, the aim of this study is to confirm the safety of ultra-HF-WBI in Japanese women. In the event that ultra-HF-WBI is confirmed to be safe, it could become a more convenient alternative to adjuvant WBI and BCS in Japan. Furthermore, we intend to follow the registered patients for at least 5 years and report the efficacy in terms of OS, PFS and IBRFS; the derived data will serve as reference ranges for the efficacy of ultra-HF-WBI in Japanese women. On the other hand, if this study fails to confirm the safety of ultra-HF-WBI in Japanese women, we will advise against the prompt introduction of this modality in clinical practice without appropriate considerations. We believe that this highly promising clinical study has the potential to positively impact the Japanese guidelines for breast cancer treatment.

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Conflict of interest statement

None declared.

Registration number

This trial has been registered in the UMIN Clinical Trials Registry as UMIN000047080 [http://www.umin.ac.jp/ctr/index.htm].

Participating institutions (arranged in alphabetical order)

Hyogo Prefectural Amagasaki General Medical Center, Japanese Red Cross Fukui Hospital, Japanese Red Cross Wakayama Medical Center, Kobe City Medical Center General Hospital, Kyoto City Hospital, Kyoto-Katsura Hospital, Kyoto Okamoto Memorial Hospital, Kyoto University Hospital, Nagahama City Hospital, Osaka Red Cross Hospital, Rakuwakai Otowa Hospital, Shiga General Hospital and Shizuoka City Shizuoka Hospital.

Contributions

All the authors were involved in designing the trial. Takamasa Mitsuyoshi, Yuka Ono, Ryo Ashida, Toshiyuki Imagumbai, Michio Yoshimura, Chikako Yamauchi, Takashi Mizowaki and Masaki

Kokubo proposed the concept and idea of this study and drafted the protocol design. Takamasa Mitsuyoshi drafted the manuscript. Sayaka Takebe, Mariko Tokiwa and Eiji Suzuki provided advice on the protocol design from the perspective of a breast surgeon. Mikiko Yamashita and Hiroaki Tanabe provided advice on quality assurance and quality control of radiation therapy from the point of view of a medical physicist. All authors have reviewed the paper and have approved the submission of this version of the manuscript.

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