Cancer Research and Oncology: Open Access
Received: Feb 18, 2016, Accepted: Apr 07, 2016, Published: Apr 11, 2016
Cancer Res Oncol, Volume 2, Issue 2
http://crescopublications.org/pdf/crooa/CROOA-2-014.pdf
Article Number: CROOA-2-014

Research Article **Open Access**

Possible Adverse Events of Non-Surgical Breast-Conserving Treatment (KORTUC-BCT) Using a New Radiosensitization Method (KORTUC II) for Patients with Stage I or II Breast Cancer

Nobutaka Aoyama[1], Yasuhiro Ogawa[2*], Hitomi Iwasa[1], Michiko Tadokoro[1], Tomoaki Yamanishi[1], Taiji Tamura[1], Kana Kobayashi[1], Shinji Kariya[1], Mitsuhiko Miyamura[3] and Takuji Yamagami[1]

[1]Department of Diagnostic Radiology and Radiation Oncology, Medical School, Kochi University, Nankoku, Kochi 783-8505, Japan

[2]Hyogo Prefectural Kakogawa Medical Center, Kakogawa, Hyogo 675-8555, Japan

[3]Department of Pharmacy, Medical School Hospital, Kochi University, Kochi, Japan

***Corresponding Author:** Yasuhiro Ogawa, Hyogo Prefectural Kakogawa Medical Center, Kakogawa, Hyogo 675-8555, Japan; Tel: +81-79-497-7001; Fax: +81-79-438-3757; E-mail: ogaway@kochi-u.ac.jp

Citation: Nobutaka Aoyama, Yasuhiro Ogawa, Hitomi Iwasa, Michiko Tadokoro, Tomoaki Yamanishi, Taiji Tamura, Kana Kobayashi, Shinji Kariya, Mitsuhiko Miyamura and Takuji Yamagami (2016) Possible Adverse Events of Non-Surgical Breast-Conserving Treatment (KORTUC-BCT) Using a New Radiosensitization Method (KORTUC II) for Patients with Stage I or II Breast Cancer. Cancer Res Oncol 2: 014.

Abstract:

The purpose of the present study was to evaluate the possible adverse events related to non-surgical breast-conserving treatment (KORTUC-BCT) using a new radio sensitization method (KORTUC II) for patients with stage I or II breast cancer. KORTUC II is a simple radiation sensitizing technique that involves injection of a solution of hydrogen peroxide and sodium hyaluronate directly into tumors prior to radiation therapy. Though over 500 cancer patients have received this therapy in Japan so far, the increase in the number of patients undertaking KORTUC II has been limited despite its remarkable therapeutic effect. Therefore, in order that this therapy can be widely used globally, it is essential to complete well-designed randomized clinical trials in the near future. Prior to the start of randomized clinical trials of KORTUC II, it is important to elucidate possible adverse events related to KORTUC II radio sensitization treatment to ensure the safety of the treatment. According to the strategy mentioned above, possible adverse events related to the treatment were analyzed in this study with the data of 72 patients with early-stage breast cancer described in our previous paper.

Treatment was well tolerated with minimal adverse effects in all 72 patients. Concerning possible adverse events related to the treatment, 29 of 72 patients showed mild impairment of liver function or kidney function on blood testing during the pre-treatment and post-treatment periods. However, there were no clinical conditions that required treatment, and no prominent general symptoms were experienced. Therefore, it was concluded that there was no relationship between KORTUC II treatment and impairment of liver or kidney function. The patients were evaluated as having at most Grade I complications (CTCAE criteria Version 4.0). It was concluded that adverse events of the treatment were within the acceptable range. In conclusion, KORTUC II radio sensitization treatment, which has

three major characteristics: imaging guidance, enzyme-targeting and targeting of breast cancer stem cells via the CD44, can be safely performed for breast cancer patients.

Keywords: Hydrogen peroxide; Sodium hyaluronate; KORTUC II; Radio sensitizer; Breast cancer; Adverse event; Ultrasonographic guidance.

1. Introduction

Though we have shown in our previous paper [1] that non-surgical breast-conserving therapy (BCT) can be performed using KORTUC II, which has three major characteristics, imaging guidance, enzyme-targeting and targeting of breast cancer stem cells via the CD44, it is essential to elucidate possible adverse events of the treatment in order that this therapy can be widely used globally. In contrast to standard methods of treatment accepted in an updated guideline, almost all physicians are apprehensive regarding introduction of a new treatment such as KORTUC II radio sensitization treatment into their clinical practice in terms of possible risks related to the treatment for both the patients and the physicians. Actually, we have already shown compelling clinically complete response (cCR) and survival rates of the treatment mainly for patients with locally advanced neoplasms and metastases [2-15]. The purpose of the present study was to evaluate the possible adverse events related to non-surgical BCT using KORTUC II radio sensitization treatment for Stage I and Stage II breast cancer, in terms of identifying possible adverse events originating from the KORTUC II radio sensitization treatment for patients without complicated physical disorders.

2. Patients and Methods

Patients and methods were described in detail in the accompanying paper [1].

A new radio sensitizing agent containing 0.5% w/v hydrogen peroxide and 0.83% w/v sodium hyaluronate (a CD44 ligand) has been developed for intra-tumoral injection into various tumors. This new method, named KORTUC II, was approved by our local ethics committee of Kochi Medical School for the treatment of breast cancer, metastatic lymph nodes, malignant melanoma, and soft tissue sarcoma, etc.

A total of 72 early-stage breast cancer patients (stage 0, 1 patient; stage I, 23; stage II, 48) were enrolled in the KORTUC II trial after providing fully informed consent at Kochi Medical School Hospital between October 2006 and September 2013 (Table 1). The patients' mean age was 59.7 years, and they were all female. Patients were eligible for the study if they had an early-stage breast cancer and had either contraindications to general anesthesia due to significant comorbidity or had declined surgical treatment and requested KORTUC II treatment.

A risk category was assigned to each patient according to the updated St. Gallen consensus based on clinical tumor size and the pathological results of a core needle biopsy taken before therapy.

After obtaining written, informed consent from the patients, non-surgical radio sensitization treatment with KORTUC II was performed, and the therapeutic effect was evaluated by PET-CT, breast MRI, ultrasonographic examination, and mammography at approximately 4 months and approximately 10 months after KORTUC II; these examinations were then repeated biannually for at least 5 years after KORTUC II treatment.

For radiation therapy, treatment planning was performed using Pinnacle^3, and hypo fraction radiotherapy was administered using a tangential fields approach including an ipsilateral axillary region and field-in-field method. The energy level was 4 MV, and the total dose was 44 Gy administered as 2.75 Gy/fraction. An electron boost of 3 Gy was added three times just following the 14th, 15th, and 16th administrations of X-ray irradiation, using an electron beam of appropriate energy for each individual patient.

A maximum of 6 mL (usually 3 mL for tumors of less than approximately 3 cm in diameter) of the agent consisting of 0.5% w/v hydrogen peroxide and 0.83% w/v sodium hyaluronate was injected into breast tumor tissue twice a week (Monday and Thursday) under ultrasonographic guidance, just prior to each administration of radiation therapy. The injection was started immediately prior to the 6th fraction of radiation therapy to avoid possible increased migration of viable tumor cells into micro vessels surrounding tumor tissue.

Concerning intratumoral injection of the agent, the injection was performed gradually, moving the depth and direction of the needle tip to obtain homogeneous distributions of micro bubbles throughout the tumor under ultrasonographic guidance. At approximately three hours after injection of the agent, a CT study was occasionally performed to ascertain the distribution of micro bubbles of oxygen produced by degradation of hydrogen peroxide by the inactivation of the anti-oxidative enzyme peroxidase.

2.1. Formulation Example

A syringe (2.5 mL) of a hyaluronic acid preparation having a 1% w/v concentration of sodium hyaluronate (ARTZ Dispo, Seikagaku Corporation, Tokyo, Japan) was used. This contained 25 mg of sodium hyaluronate, 2.5 mg of L-methionine, sodium chloride, potassium phosphate, crystalline sodium dihydrogen phosphate, and an isotonizing agent. The preparation is a colorless, transparent, viscous, aqueous solution having a pH of 6.8 to 7.8, specific osmotic pressure of 1.0 to 1.2 (relative to physiological saline), and a weight-average molecular weight of 600,000 to 1.2 million. To this, 0.5 mL of a 3% w/v solution of hydrogen peroxide (Oxydol, Ken-ei Pharmaceutical Co. Ltd., Osaka, Japan) was added immediately before use and mixed well to prepare the radio sensitizer. Hydrogen peroxide, as a small vial containing 0.5 mL of 3% w/v hydrogen peroxide, was aseptically prepared and kindly provided to us by the Department of Pharmacy, Kochi Medical School Hospital. The sensitizer has a sodium hyaluronate concentration of 0.83% w/v and a hydrogen peroxide concentration of approximately 0.5% w/v. This preparation was used in the study.

2.2. Patient Assessment (Primary Breast Tumor and Toxicity of Therapy)

Patient assessment was described in detail in the accompanying paper [1].

Tumor response was assessed according to the Revised Response Evaluation Criteria In Solid Tumors (RECIST) criteria [15] using CE-breast magnetic resonance imaging (MRI), FDG-positron emission tomography-computed tomography (PET-CT), and ultrasonography. Patients were assigned a toxicity grade from a standard assessment scale (NIH common toxicity criteria). Treatment-related complications were assessed in detail in order to evaluate the feasibility of this approach. The patients underwent PET-CT and/or dynamic MRI examinations before and approximately 4 months after KORTUC II treatment, and every 6 months thereafter if possible for at least 5 years. Patient monitoring and tumor assessment were performed once a month. Patients were assigned a toxicity grade from a standard assessment scale (National Institutes of Health Common Toxicity Criteria). Treatment-related complications were assessed in detail to evaluate the feasibility of the approach according to the Common Terminology Criteria for Adverse Events (CTCAE criteria Version 4.0). Patients were followed for at least 12 months.

3. Results

Treatment was well tolerated with minimal adverse effects in all 72 patients.

As an acute toxicity related to KORTUC II, 7 patients complained of strong local pain at the injection site early during the trial, and the pain continued for several hours following injection of the agent. On the basis of their experience of local pain, combined use of approximately 0.5 mL of 1% w/v lidocaine with the KORTUC injection was started as of March 2008, and since then, none of the remaining 65 patients has complained of strong local pain. There were no patients who experienced pain on the day of after injection.

According to the progress of radiotherapy, all patients showed mild dermatitis: Grade I, 45 patients; Grade II, 27 patients. They were all cured by symptomatic treatment or without any treatment.

Concerning possible adverse events of the treatment, 29 of 72 patients showed mild impairment of liver function or kidney function on blood testing during the pre-treatment and post-treatment periods. However, there were no clinical conditions that required treatment. Concerning respiratory system complications such as pulmonary embolism that can result from the degradation of hydrogen peroxide into water and oxygen in blood vessels, there were no patients who showed abnormal findings on chest CT and/or X-ray examinations during treatment and 6 months after treatment. No patients had prominent general symptoms. There was no evidence of a relationship between KORTUC II treatment and impairment of liver and/or kidney function. The patients were evaluated as having at most Grade I complications (CTCAE criteria Version 4.0). A summary of the patients' data and treatment progress is shown in Table I. The details of the adverse events before, during, and following KORTUC II treatment are shown in Tables II and III. Consequently, no characteristic adverse events directly related to KORTUC II radio sensitization treatment were identified.

Table I: Summary of the patients' data.

Pt.	Age (y)	Hormone receptor			Disease Site	cTNM	Exposure dose (Gy)	Induction Chemotherapy	Therapeutic effects	Prognosis (y: years)
		ER	PgR	HER 2						
1	88	(+)	ND	ND	Rt.E	cT2N1M0	53	(-)	cCR	NED > 7.0 y
2	78	(+)	ND	ND	Rt.D	cT2N0M0	53	(-)	cCR	NED > 8.0 y

3	79	(+)	(+)	(-)	Lt.B & Rt.C	cT2N0M0 cT1cN0M0	53 53	(-) (-)	cPR cCR	Dead at 6.5 y
4	59	(+)	ND	ND	Lt.E	cT2N0M0	53	(-)	cCR	NED for 7.3 y
5	49	(+)	(+)	(+)	Rt.CD	cT2N0M0	53	EC×4	cCR	NED for 8.1 y
6	73	(+)	(+)	(+)	Lt.C	cT1cN0M0	53	(-)	cCR	NED for 7.3 y
7	79	(+)	(+)	(+)	Lt.CD	cT2N0M0	49.5	(-)	cCR	NED for 4.5 y
8	60	(+)	ND	ND	Rt.A	cT2N1M0	53	EC×6	cCR	NED for 7.3 y
9	77	(+)	(+)	(+)	Rt.ADB	cT2N0M0	49.5	(-)	cCR	NED for 7.0 y
10	82	(+)	(+)	(+)	Rt.ABE	cT2N0M0	53	(-)	cCR	NED for 7.0 y
11	63	(+)	(+)	(+)	Lt.C	cT2N0M0	53	(-)	cCR	NED for 7.2 y
12	52	(-)	(-)	(-)	Rt.AB	cT2N1M0	53	EC×4	cCR	NED for 6.9 y
13	87	(+)	(+)	(+)	Lt.C	cT1cN0M0	53	(-)	cCR	NED for 6.8 y
14	63	(+)	ND	(-)	Rt.A	cT1cN0M0	53	(-)	cCR	NED for 6.8 y
15	42	(+)	ND	(-)	Rt.ECD	cTisN0M0	49.5	(-)	cCR	NED for 6.5 y
16	61	(+)	(+)	(-)	Rt.B	cT1cN0M0	53	(-)	cCR	NED for 6.4 y
17	60	(-)	(-)	(+)	Rt.D	cT1cN0M0	53	(-)	cCR	NED for 6.3 y
18	80	(+)	(+)	(+)	Rt.C	cT2N1M0	53	(-)	cCR	NED for 6.3 y
19	43	(+)	(+)	(-)	Lt.B & E	cT2N0M0	49.5	FEC×4	cCR	NED for 6.3 y
20	42	ND	ND	ND	Lt.C	cT2N0M0	53	FEC×4	cCR	NED for 6.1 y
21	77	(+)	(+)	(-)	Lt.AE	cT1cN1M0	53	(-)	cCR	NED for 6.1 y
22	47	(+)	(+)	(-)	Rt.AC	cT2N0M0	53	EC×4	cCR	NED for 6.1 y
23	47	(+)	(-)	(+)	Lt.BDE	cT2N0M0	53	EC×4 + TXT×4	cCR	NED for 6.1 y
24	50	(+)	(+)	(+)	Rt.AB	cT1cN0M0	53	(-)	cCR	NED for 5.7 y
25	67	(+)	(+)	(+)	Lt.D	cT2N0M0	53	EC×4	cCR	NED for 6.0 y
26	49	(+)	(+)	(-)	Lt.CD	cT2N0M0	53	EC×4 + TXT×4	cCR	NED for 6.0 y
27	43	(+)	ND	(-)	Rt.C	cT1cN0M0	53	(-)	cCR	NED for 5.7 y
28	76	(+)	(+)	(-)	Lt.C	cT1bN0M0	53	(-)	cCR	NED for 5.7 y
29	45	(+)	(+)	(-)	Rt.E	cT2N0M0	53	EC×4	cCR	NED for 5.5 y
30	81	(+)	(+)	(-)	Rt.A	cT2N0M0	53	(-)	cCR	NED for 4.8 y
31	83	(+)	(+)	(-)	Lt.B	cT2N0M0	53	(-)	cCR	NED for 5.1 y
32	68	(+)	ND	(+)	Rt.B	cT2N0M0	53	EC×4	cCR	NED for 5.1 y
33	29	(+)	(+)	(-)	Lt.C	cT1cN0M0	53	(-)	cCR	ND

34	63	(+)	(+)	(-)	Rt.CD	cT1cN0M0	53	(-)	cCR	NED for 4.6 y
35	24	(+)	(+)	(-)	Lt.A	cT1cN0M0	53	(-)	cCR	NED for 4.5 y
36	40	(+)	(-)	(-)	Rt.A	cT2N0M0	53	TC×4	cCR	NED for 4.7 y
37	59	(+)	(+)	(-)	Rt.E	cT1cN0M0	53	(-)	cCR	NED for 4.5 y
38	68	(-)	(-)	(-)	Rt.A	cT2N0M0	53	EC×4	cCR	NED for 4.6 y
39	37	(+)	(+)	ND	Rt.D	cT1cN0M0	53	(-)	cCR	NED for 4.4 y
40	49	(+)	(+)	(-)	Lt.A	cT2N0M0	53	(-)	cCR	NED for 4.1 y
41	63	(-)	(-)	(-)	Lt.C	cT2N0M0	49.5	EC×4	cCR	NED for 4.3 y
42	70	(+)	(+)	(+)	Rt.A	cT2N1M0	53	EC×4	cCR	NED for 4.1 y
43	60	(-)	(-)	(+)	Lt.A	cT1cN1M0	53	EC×4	cCR	NED for 3.9 y
44	44	(+)	(+)	(-)	Lt.C	cT2N0M0	49.5	(-)	cCR	NED for 3.7 y
45	48	(+)	(+)	(-)	Rt.C	cT1cN0M0	53	(-)	cCR	NED for 3.5 y
46	70	(+)	(+)	(-)	Rt.AB	cT1cN0M0	53	(-)	cCR	NED for 3.6 y
47	55	(+)	(-)	(-)	Rt.D	cT2N1M0	53	EC×4	cCR	NED for 3.8 y
48	69	(+)	(+)	(-)	Lt.CD	cT2N0M0	53	(-)	cCR	NED for 5.1 y
49	61	(+)	(+)	(-)	Rt.BD	cT2N1M0	53	EC×4	cCR	Bone meta.
50	61	(-)	(-)	(-)	Rt.C	cT2N1M0	49.5	EC×4 + TXT×4	cCR	NED for 3.8 y
51	59	(+)	(+)	(-)	Rt.C	cT1cN0M0	53	(-)	cCR	NED for 3.7 y
52	78	(+)	(+)	(-)	Rt.A	cT1bN0M0	53	(-)	ND	ND
53	76	(+)	(+)	(-)	Rt.AB	cT2N0M0	53	(-)	cCR	NED for 3.2 y
54	63	(+)	(+)	(-)	Lt.A	cT2N0M0	53	(-)	cCR	NED for 3.2 y
55	50	(-)	ND	(+)	Rt.A	cT2N1M0	53	FEC×4 + TXL×4	cCR	NED for 3.0 y
56	38	(+)	(-)	(+)	Lt.A	cT2N1M0	53	EC×4 + TXT×4	cCR	NED for 3.6 y
57	35	(-)	(-)	(-)	Lt.C	cT2N1M0	49.5	EC×8	cCR	NED for 3.5 y
58	56	(+)	(+)	(-)	Lt.CD	cT1cN0M0	53	(-)	cPR	NED for 2.8 y
59	79	(-)	(-)	(-)	Rt.ED	cT2N0M0	53	(-)	cCR	NED for 2.7 y
60	39	(+)	(-)	(-)	Rt.C	cT1cN0M0	53	EC×4	cCR	NED for 2.8 y
61	51	(+)	(+)	(-)	Rt.D	cT2N0M0	53	(-)	cCR	NED for 2.5 y
62	46	(+)	(+)	(-)	Lt.C	cT1cN0M0	53	(-)	cCR	NED for 2.5 y
63	47	(+)	(+)	(-)	Rt.BD	cT1cN1M0	49.5	EC×4	cCR	NED for 2.4 y
64	67	(+)	(+)	(-)	Rt.C	cT1cN0M0	53	(-)	cCR	NED for 2.4 y
65	74	(+)	(+)	(-)	Rt.C	cT2N0M0	53	(-)	cCR	NED for 2.4 y

66	63	(+)	(+)	(-)	Lt.BD	cT2N0M0	53	(-)	cCR	NED for 2.2 y
67	58	(+)	(+)	(+)	Rt.AB	cT2N0M0	53	(-)	cCR	NED for 2.1 y
68	54	(+)	(+)	(-)	Lt.A	cT1cN0M0	53	(-)	cCR	NED for 2.1 y
69	43	(+)	(+)	(-)	Lt.C	cT2N0M0	53	(-)	cCR	NED for 2.0 y
70	83	(+)	(+)	(-)	Rt.C	cT1cN0M0	53	(-)	cCR	NED for 2.2 y
71	75	(+)	(+)	(-)	Lt.C	cT2N0M0	53	(-)	cCR	NED for 1.8 y
72	39	(+)	(+)	(-)	Lt.AC	cT2N0M0	53	(-)	cCR	NED for 1.7 y

Pt.: patient, ER: estrogen receptor, PgR: progesterone receptor, HER2: human epidermal growth factor receptor type 2, RT field: Radiation therapy field, Rt.: right, Lt.: left, ND: no data, NED: no evidence of disease, CR: complete response,
EC: Epirubicin + Cyclophosphamide, TXT: Docetaxel hydrate
FEC: Fluorouracil + Epirubicin + Cyclophosphamide, TXL: Paclitaxel

Table II: Adverse events by the KORTUC II treatment.

	Age (y)	pain during the injection	pain on the next day of injection	change of blood pressure	impairment of liver function				impairment of kidney function				abnormalities of chest or abdomen			
					Pre	Under	P≦3M	P>3M	Pre	Under	P≦3M	P>3M	Pre	Under	P≦3M	P>3M
1	88	severe	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
2	78	severe	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
3	79	severe	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(-)	(-)	(+)	(-)	(-)	(-)	(-)
4	59	severe	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
5	49	severe	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
6	73	severe	(-)	(-)	(+)	(+)	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
7	79	severe	(-)	(-)	(+)	(+)	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
8	60	no data	no data	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
9	77	mild	(-)	(-)	(+)	(+)	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
10	82	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
11	63	(-)	(-)	(-)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
12	52	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
13	87	mild	(-)	(-)	(-)	(-)	(+)	(-)	(+)	(+)	(+)	(+)	(-)	(-)	(-)	(-)
14	63	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
15	42	mild	(-)	(-)	(+)	(+)	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
16	61	mild	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)

17	60	mild	(-)	(-)	(+)	(-)	(-)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
18	80	(-)	(-)	(-)	(+)	(-)	(-)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
19	43	mild	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
20	42	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
21	77	mild	(-)	(-)	(-)	(-)	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
22	47	(-)	(-)	(-)	(-)	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
23	47	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
24	50	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
25	67	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
26	49	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
27	43	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
28	76	(-)	(-)	(-)	(-)	(-)	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
29	45	(-)	(-)	(-)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
30	81	(-)	(-)	(-)	(+)	(-)	(-)	(+)	(+)	(+)	(+)	(+)	(-)	(-)	(-)
31	83	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
32	68	no data	no data	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
33	29	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
34	63	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
35	24	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
36	40	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
37	59	mild	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
38	68	(-)	(-)	(-)	(+)	(+)	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
39	37	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
40	49	mild	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
41	63	mild	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
42	70	mild	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
43	60	mild	(-)	(-)	(-)	(+)	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
44	44	mild	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
45	48	mild	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
46	70	mild	(-)	(-)	(+)	(-)	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
47	55	mild	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
48	69	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)

49	61	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
50	61	(-)	(-)	(-)	(+)	(-)	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
51	59	(-)	(-)	(-)	(-)	(-)	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
52	78	mild	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
53	76	mild	(-)	(-)	(+)	(+)	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
54	63	mild	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
55	50	no data	no data	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
56	38	mild	(-)	(-)	(+)	(+)	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
57	35	mild	(-)	(-)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
58	56	mild	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
59	79	mild	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
60	39	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
61	51	mild	(-)	(-)	(+)	(+)	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
62	46	mild	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
63	47	mild	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
64	67	mild	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
65	74	(-)	(-)	(-)	(+)	(-)	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
66	63	(-)	(-)	(-)	(-)	(-)	(-)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
67	58	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
68	54	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
69	43	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
70	83	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
71	75	(-)	(-)	(-)	(-)	(-)	(+)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)
72	39	(-)	(-)	(-)	(+)	(+)	(-)	(+)	(-)	(-)	(-)	(-)	(-)	(-)	(-)	(-)

Pre: pretreatment, Under: under treatment, P<3M: post treatment <3 months

P>3M: post treatment >3 months

Table III: Detailed impairment of liver function and kidney function (MAX-value).

Pt.	Pre	Under	Post≦3M	Post＞3M
3	(-)	no data	(-)	BUN：27, CK：292
				LDH：254
7	LDH：386, CK：491	no data	LDH：245, CK：230	LDH：342, CK：428
11	LDH：266, T-CHO：272	no data	(-)	(-)
12	T-CHO：301	no data	T-CHO max：267	T-CHO max：307
13	CRE：1.67	CRE：1.03	CRE：1.24	CRE：1.42
	BUN：36	BUN：22	BUU：27	BUN：35
			CK：428	
14	ALP：367	(-)	ALP：399	ALP：838, ALT：45
			ALT：41	AST：45, CK：193
			AST：41	LDH：241,
15	γ-GTP：76	γ-GTP：88	γ-GTP：102	γ-GTP：118
17	ALT：67, AST：40	no data	(-)	ALT：45, AST：36
18	ALT：71, AST：76	no data	ALP：410	ALP：555, ALT：61
	γ-GTP max：143		AST：41	AST：69, γ-GTP：86
21	(-)	no data	CK：186, LDH：234	CK：359, LDH：266
22	ALT：57, AST：41	no data	ALT：132, AST：97	(-)
			LDH：253	
28	(-)	no data	CHE：520, T-CHO：279	CHE：562, T-CHO：267
29	CHE：636	no data	(-)	(-)
30	CK：198, BUN：28	BUN：26	BUN：32	BUN：34
	CRE：1.09	CRE：1.19	CRE：1.2	CRE：1.08
31	BUN max：25	no data	BUN：24	ALP：791, ALT：97
				AST：89, BUN：24
				γ-GTP：327
38	(-)	no data	(-)	γ-GTP：71
43	ALT：99, AST：74	AST：42	ALP：444, ALT：67	ALP：371, AST：38
	γ-GTP：85	γ-GTP：75	AST：59	CK：611, LDH：353

			γ-GTP max：98	T-CHO：420
46	LDH：322	no data	ALP：346, LDH：311	ALP：435, LDH：295
	CK：449		T-CHO：253	T-CHO：254
50	CK：175, LDH：272	no data	LDH：225	CK：205, LDH：251
51	ALT：51, AST：36	no data	ALT：73	ALT：89
			AST：48	AST：76
			CK：226	CK：241
				LDH：241
53	CK：208	no data	ALT：52, AST：55	ALT：55, AST：55
	LDH：284		CK：284, LDH：234	CK：375, LDH：286
				γ-GTP：100
56	ALT：60	no data	ALT：36	ALP：380
	CHE：480		LDH：276	ALT：77
	LDH：276			AST：45
				LDH：258
57	ALT：41, AST：34	(-)	(-)	(-)
	LDH：244, γ-GTP：58			
58	(-)	no data	(-)	ALT：73, AST：56
				CK：221, LDH：267
61	ALP：392	ALP：345	γ-GTP：53	CK：356, γ-GTP：92,
63	(-)	(-)	(-)	LDH：242, T-CHO：226
65	ALT：48, AST：44	no data	ALT：37, AST：46	ALT：47, AST：49
				LDH：245
71	(-)	LDH：253	CHE：483	CHE：503, LDH：273
72	CK：753	CK：179	(-)	CK：230

ALT: alanine aminotransferase, ALP: alkaline phosphatase, AST: aspartate aminotransferase

BUN: blood urea nitrogen, CHE: cholinesterase, CK: creatine kinase, CRE: creatinine

LDH: lactate dehydrogenase, T-CHO: total cholesterol, γ-GTP: γ-glutamyl transpeptidase

4. Discussion

Hydrogen peroxide increases the oxygen tension in what is typically a hypoxic intra-tumor environment by the oxygen molecules produced by degradation of hydrogen peroxide into water and oxygen brought about the catalytic reaction of anti-oxidative enzymes such as peroxidase and/or catalase in tumor tissues and/or normal tissues. At the same time as the degradation of hydrogen peroxide occurs, the activities of peroxidases and/or catalase are inactivated.

Actually, we have already shown our preliminary therapeutic results of KORTUC-BCT [1-3,7], non-surgical chemo-radio sensitization treatment for locally advanced breast cancer (KORTUC-LABC) [8,9], electron-radio sensitization for lesions with local recurrence (KORTUC-REC) [10,11], including post-radiotherapy lesions, and intra-operative radio sensitization treatment for locally-advanced stage IVa pancreatic carcinoma (KORTUC-IOR) [14]. These well-characterized patient series data showed compelling complete remission and survival rates.

To demonstrate this clearly, it is essential to conduct well-designed randomized clinical trials in Western countries, as well as in Japan. However, before doing so, we considered that it was very important to elucidate possible adverse events related to KORTUC II radio sensitization treatment. Therefore, we analyzed the data of early-stage breast cancer patients recently reported in our previous paper in terms of identifying possible adverse events more clearly than the data of locally advanced or recurrent breast cancer patients whose data have frequently shown deterioration of blood tests and/or urine analyses or physical examinations using various diagnostic modalities, due to complicating physical symptoms brought about by many kinds of local and/or systemic treatments already performed for these patients before the beginning of KORTUC II radio sensitization treatment.

Actually, KORTUC II is a very safe method of radio sensitization in terms of the application of the essential body components of hydrogen peroxide and sodium hyaluronate to augment the therapeutic effect of radiotherapy and/or chemotherapy, and the safety of KORTUC II is considered to have been more clearly demonstrated.

KORTUC II is considered to be a very favorable procedure in that it incurs fewer costs, maximally utilizing radical reactions, which compose two-thirds of the therapeutic effect of Linac X-rays and/or electrons.

When using the agent, it is essential to avoid direct injection of the agent into blood vessels and to confirm even distribution of oxygen micro bubbles throughout the tumor tissue using ultrasonographic or CT guidance, to avoid oxygen embolism. Actually, no patients showed abnormalities such as pulmonary embolism on chest CT and/or chest X-ray examinations at the start of KORTUC II radio sensitization treatment and 6 months following the treatment. Concerning blood and urine analyses, no patients showed abnormalities directly related to the KORTUC II injection. Therefore, it was concluded that KORTUC II was a totally safe therapeutic modality for patients with breast cancer.

Because KORTUC II is safe and effective, as well as remarkably less expensive than other methods, it has great potential to become a viable non-invasive replacement for surgical procedures and a valuable radio sensitization method for most low LET-radio resistant neoplasms.

5. Conclusions

It was concluded that adverse events of the KORTUC II treatment for patients with stage I or II breast cancer were within the acceptable range. Therefore, KORTUC II radio sensitization treatment, which has three major characteristics: imaging guidance, enzyme-targeting and targeting of breast cancer stem cells via the CD44, can be safely performed for breast cancer patients, and randomized clinical trials in Western countries, as well as in Japan should be conducted to clearly demonstrate the therapeutic efficacy of KORTUC II in the near future.

Acknowledgments

This work was partially supported by a grant-in-aid for Scientific Research from the Japanese Ministry of Education, Culture, Sports, Science and Technology (25461916).

Author Contributions:

Nobutaka Aoyama and Yasuhiro Ogawa contributed to the study concept, clinical study design, and data analysis and manuscript preparation. Yasuhiro Ogawa also contributed to injection of the KORTUC agent. Nobutaka Aoyama and Hitomi Iwasa contributed to imaging guidance by ultrasonography. Tomoaki Yamanishi and Taiji Tamura contributed to obtaining a core needle biopsy. Kana Kobayashi and Shinji Kariya contributed to treatment planning of radiation therapy. Michiko Tadokoro and Takuji Yamagami contributed to interpretations of diagnostic examinations. Mitsuhiko Miyamura contributed to preparation of the KORTUC agent.

References

1. Ogawa, Y.; Kubota, K.; Aoyama, N.; Yamanishi, T.; Kariya, S.; Hamada, N.; Nogami, M.; Nishioka, A.; Onogawa, M.; Miyamura, M. Non-surgical breast-conserving treatment (KORTUC-BCT) using a new radiosensitization method (KORTUC II) for patients with stage I or II breast cancer. Cancers 2015, 7: 2277-2289.

2. Yaogawa, S.; Ogawa, Y.; Morita-Tokuhiro, S.; Tsuzuki, A.; Akima, R.; Itoh, K.; Morio, K.; Yasunami, H.; Onogawa, M.; Kariya, S.; Nogami, M.; Nishioka, A.; Miyamura, M. Serial assessment of therapeutic response to a new radiosensitizationtreatment, Kochi Oxydol-Radiation Therapy for Unresectable Carcinomas, Type II (KORTUC II), in patients with stage I/II breast cancer using breast contrast-enhanced magnetic resonance imaging. Cancers2016, 8: 1.

3. Tsuzuki, A.; Ogawa, Y.; Kubota, K.; Tokuhiro, S.; Akima, R.; Yaogawa, S.; Itoh, K.; Yamada, Y.; Sasaki, T.; Onogawa, M.; et al. Evaluation of changes in tumor shadows and microcalcifications on mammography following KORTUC II, a new radiosensitization treatment without any surgical procedure for elderly patients with stage I and II breast cancer. Cancers 2011, 3: 3496–3505. [CrossRef] [PubMed].

4. Ogawa, Y.; Kubota, K.; Ue, H.; Kataoka, Y.; Tadokoro, M.; Miyatake, K.; Tsuzuki, K.; Yamanishi, T.; Itoh, S.; Hitomi, J.; et al. Phase I study of a new radiosensitizer containing hydrogen peroxide and sodium hyaluronate for topical tumor injection: A new enzyme-targeting radiosensitization treatment, Kochi Oxydol-Radiation Therapy for Unresectable Carcinomas, Type II (KORTUC II). Int. J. Oncol. 2009, 34: 609–618. [CrossRef] [PubMed].

5. Ogawa, Y.; Kubota, K.; Ue, H.; Tadokoro, M.; Matsui, R.; Yamanishi, T.; Hamada, N.; Kariya, S.; Nishioka, A.; Nakajima, H.; et al. Safety and effectiveness of a new enzyme-targeting radiosensitization treatment (KORTUC II) for intratumoral injection for low-LET radioresistant tumors. Int. J. Oncol. 2011, 39: 553–560. [CrossRef] [PubMed].

6. Ogawa Y, Kubota K, Ue H, Nishioka A, Kariya S, Yokota N, Sasaki T, Suzuki K, Nakatani K, Yamanishi T, et al: Development and clinical application of a new radio sensitizer containing hydrogen peroxide and hyaluronic acid sodium for topical tumor injection― a new enzyme-targeting radio sensitization treatment, KORTUC II (Kochi Oxydol-Radiation Therapy for Unresectable Carcinomas, Type II). Strahlenther Onkol 183: 100-101, 2007.

7. Hitomi J, Kubota K, Ogawa Y, Hamada N, Murata Y and Nishioka A: Non-surgical therapy and radiologic assessment of stage I breast cancer treatment with novel enzyme-targeting radio sensitization: Kochi Oxydol-Radiation Therapy for Unresectable Carcinomas, type II (KORTUC II). Exp Ther Med 5: 769-775, 2010.

8. Miyatake K, Kubota K, Ogawa Y, Hamada N, Murata Y and Nishioka A: Non-surgical care for locally advanced breast cancer: Radiologically assessed therapeutic outcome of a new-enzyme-targeting radio sensitization treatment, Kochi Oxydol-Radiation Therapy for Unresectable Carcinomas, Type II (KORTUC II) with systemic chemotherapy. Oncol Rep 24: 1161-1168, 2010.

9. Simbo, T.; Yoshikawa, N.; Yoshioka, H.; Tanaka, Y.; Yoshida, K.; Uesugi, Y.; Narumi, Y.; Inomata, T. Three cases of unresectable locally advanced breast cancer treated with local injection of the new radio sensitization (KORTUC). Rinsho Hoshasen (Japan. J. Clin. Radiol.), 2013, 58(13), 1881-1886 (in Japanese with English abstract).

10. Aoyama N, Ogawa Y, Kubota K, Ohgi K, Kataoka Y, Miyatake K, Tadokoro M, Yamanishi T, Ohnishi T, Hamada N, et al: Therapeutic response to a new enzyme-targeting radio sensitization treatment (KORTUC-SC) for patients with recurrent breast cancer. J Cancer Res Ther 1: 215-219, 2013.

11. Aoyama N, Ogawa Y, Kubota K, Miyatake K, Tadokoro M, Yamanishi T, Hamada N, Tamura T, Nishioka A, Onogawa M, et al: Therapeutic response to a new enzyme-targeting radio sensitization treatment (Kochi Oxydol Radiation Therapy for Unresectable Carcinomas) in patients with recurrent breast cancer. Oncol Lett 2016 (in print).

12. Aoyama N, Ogawa Y, Yasuoka M, Iwasa H, Miyatake K, Yoshimatsu R, Yamanishi T, Hamada N, Tamura T, Kobayashi K et al. Therapeutic response to a new enzyme-targeting radio sensitization treatment (KORTUC II) for residual lesions in patients with Stage IV primary breast cancer following induction chemotherapy with epirubicin + cyclophosphamide and/or taxane. Oncol Lett 2016 (in print).

13. Aoyama N, Ogawa Y, Nishimori M, Ohgi K, Iwasa H, Miyatake K, Yoshimatsu R, Yamanishi T, Hamada N, and Tamura T, et al. Therapeutic results of a new enzyme-targeting radio sensitization treatment (Kochi Oxydol-Radiation Therapy for Unresectable Carcinomas II, KORTUC II) in patients with Stage I primary breast cancer. Oncol Lett 2016 (in print).

14. Nishioka A, Ogawa Y, Miyatake K, Tadokoro M, Nogami M, Hamada N, Kubota K, Kariya S, Kohsaki T, Saibara T, Okabayashi T, Hanazaki K. Safety and efficacy of image-guided enzyme-targeting radio sensitization and intraoperative radiotherapy for locally advanced unresectable pancreatic cancer. Oncol Lett 2014, 8(1), 404-408.

15. Obata, S.; Yamanishi, M.; Katsumi, S.; Ohta, Y.; Kan, T.; Kanegae, S.; Inoue, Y.; Kuroiwa, A.; Inoue, K.; Watanabe, K.; et al. A new treatment strategy for advanced rectal cancer: enzyme-targeting and radio-sensitization treatment, so-called KORTUC (Kochi-Oxydol Radiation Therapy for Unresectable Carcinomas). Nagasaki Igakkai Zasshi 2015, 90(2), 135-145 (in Japanese with English abstract).