Original Article Open Access

Archives Of Breast Cancer

DOI: 10.32768/abc.202182149-155

Preliminary Report of Partial-breast Irradiation Following Neoadjuvant Chemotherapy from COMBAT-NEO: Clinical Outcome of Multicatheter BrAchyTherapy after NEOadjuvant Chemotherapy

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ARTICLE INFO

Received:
16 March 2021
Revised:
24 March 2021
Accepted:
01 April 2021

Key words:
Breast cancer,
breast conserving therapy,
partial breast irradiation,
neoadjuvant chemotherapy,
multicatheter interstitial
brachytherapy

ABSTRACT

Background: Breast-conserving therapy (BCT) with partial-breast irradiation (PBI) has become a standard alternative to whole-breast irradiation. Recently, neoadjuvant chemotherapy (NACT) has been widely performed for early breast cancer. Although BCT using perioperative PBI decreased invasiveness and geographic miss, risks of adverse events and local recurrence remain a concern for patients receiving NACT. Thus, a prospectively registered study, the Clinical Outcome of Multicatheter BrAchyTherapy after NEOadjuvant chemotherapy (COMBAT-NEO), was conducted.

Methods: Patients who underwent BCT using multicatheter-interstitial brachytherapy (MIB) by intraoperative catheter implant were analyzed. Early and late adverse events (AEs) including higher grade skin toxicities and wound complications, and tumor control of patients receiving NACT were evaluated in comparison with adjuvant chemotherapy (ACT) and no chemotherapy (no-CT).

Results: Between April 2017 and February 2020, 265 consecutive patients who received single-stage BCT were evaluated, including 13 NACT (4.9%), 68 ACT (25.7%), and 184 no-CT (69.4%). The median follow-up time and age were 30.0 months and 59.0 years, respectively. All patients were followed up for at least 12 months. Although AEs in NACT, ACT, and no-CT were observed in 1 (7.7%), 5 (7.4%), and 11 (6.0%) patients, respectively ($p = 0.91$) and there was no acute AE in NACT patients. Overall, 3 (1.1%) ipsilateral and 1 (0.4%) contralateral breast tumor recurrences were observed in no-CT patients. There were no regional and distant recurrences.

Conclusion: Although this pilot study was based on a small sample size with short follow-up, these preliminary results support the study of a single-stage BCT with MIB-PBI following NACT.

Introduction

In recent years, partial-breast irradiation (PBI) has become a standard adjuvant radiation treatment for breast-conserving therapy (BCT), acting as an alternative method to whole-breast irradiation (WBI) in patients with low risk breast cancer.[1] Among established PBI techniques, multicatheter-interstitial brachytherapy (MIB) has been supported by randomized controlled trials.[2,3] It is a useful technique especially for patients with small breasts because of a high conformity to the cavity and a limited normal tissue exposure.[4] Careful patient selection combined with modern imaging studies and perioperative

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partial-breast brachytherapy by intraoperative catheter implant could allow single-stage BCT.[5, 6, 7] Despite the advantages of decreased invasiveness and less geographic miss, some concerns regarding this single-stage BCT include radiation toxicity and surgical complications because this may produce a negative impact on wound recovery.[8]

In general, systemic therapy using cytotoxic chemotherapy has been incorporated as a multidisciplinary approach, not only to improve breast cancer-specific survival, but also to reduce local recurrences.[9] The indication and therapeutic regimen of chemotherapy after surgery were considered on the basis of the postoperative pathology as an adjuvant chemotherapy (ACT). When ACT was conducted before surgery as a neoadjuvant chemotherapy (NACT), more patients could undergo BCT with better cosmesis due to tumor shrinkage.[10] Recently, NACT has been increasingly performed for patients in order to obtain the desired therapeutic response and consider an additional ACT.[11,12,13]

In our institution, single-stage BCT using MIB-PBI has been performed by intraoperative catheter implant, and has showed excellent local control with adequate toxicity.[14] Although it was not clear whether there was an increased risk of local recurrence or adverse events on BCT using WBI after NACT[15], clinical outcomes with PBI remain unknown. Therefore, a single-center prospective registered trial, Clinical Outcome of Multicatheter BrAchyTherapy for partial-breast irradiation after NEOadjuvant chemotherapy in breast cancer patients (COMBAT-NEO), was conducted to investigate the toxicity, tumor control, and cosmetic outcomes for patients receiving perioperative MIB-PBI after NACT. Here, the preliminary results of early and late adverse events (AEs) and tumor control in 13 patients were reported in comparison to patients undergoing MIB-PBI during the same period of time.

Methods

Study design and patient eligibility

Patients with histologically confirmed breast cancer of stages I and II were eligible when meeting the following criteria: female, age of 40 years or older, candidates for breast-conserving surgery (BCS) without NACT, and a 3 cm or less maximum tumor diameter after NACT. Patients with positive axillary nodes before NACT were included, but axillary dissection was conducted in all patients irrespective of the response to NAC. Written informed consent was obtained from all patients who wished to participate in this study after completion of NACT. After MIB-PBI, patients were allowed to receive an additional WBI based on the final pathology, who were included for the analysis. Firstly, 20 patients were enrolled for the detailed analysis of early AEs from the perspective of safety and more candidates were included for the evaluation of late AEs and tumor control. Preoperative patient workup including standard laboratory parameters, mammography, and ultrasonography as well as contrast-enhanced magnetic resonance imaging (MRI) of the breast and axilla was included. In general, an ultrasound visible clip (HydroMARK™: Mammotome, Cincinnati, OH) was placed for patients who planned to receive NAC. Patients with an axillary node suspected for metastasis underwent axillary fine-needle aspiration. When the nodal metastasis was confirmed by fine-needle aspiration, an axillary dissection was performed with or without NACT.

This study was designed as a prospective single-institutional phase II trial. After approval by the Central Ethics Committee of the Tokushukai Medical Group, registration started in April 2017.

Technique of single-stage BCT using MIB-PBI

BCS was performed by the removal of the tumor with a 1.0-cm gross margin using a moving incision to prevent direct radiation exposure to the wound.[16] After confirmation of a negative surgical margin by specimen mammography, rigid steel needles were placed to act as a reference in dosimetric planning for preoperative contrast-enhanced computed tomography (CT).[17] Plastic tubes were replaced by steel needles to introduce the Iridium-192 brachytherapy source. After surgery, patients received a postoperative CT for treatment planning of MIB-PBI with Oncentra Brachy (ver. 4.5.1. Elekta, Stockholm, Sweden).

The clinical target volume (CTV) was created with 1.0-cm margins beyond the delineated cavity. Planning target volume (PTV) was equal to the CTV. The PTV (PTV_EVAL) was set at 5 mm under the skin and the surface of the pectoral muscle as superior and deep margins, respectively. A total dose of 32 Gy in 8 fractions was delivered on 4 consecutive working days, twice a day with at least 6-hour intervals. At least 90% of the PTV_EVAL was covered with 90% of the prescribed dose (PD). The dose limits were as follows: volume receiving 150% of PD (V150%) $\leq$70 cm^3, V200% $\leq$20 cm^3, maximal skin and chest wall dose ideally <75% PD, and strictly <100% PD in our protocol.[14] All patients received antibiotics during catheter implantation. Catheters were removed immediately after the final radiotherapy.

Chemotherapeutic regimens

In general, NACT regimens were implemented from the standard regimens of ACT. Most patients started with a chemotherapeutic regimen consisting of AC (adriamycin/cyclophosphamide: 60/600 mg/m^2) x4 intravenously (IV) every 2 weeks followed by paclitaxel (80 mg/m^2) x12 IV every week[18], or TC (docetaxel/cyclophosphamide: 60/600 mg/m^2) x4 IV every 3 weeks.[19] Trastuzumab (8

mg/kg loading dose followed by 6 mg/kg every 3 weeks) and pertuzumab (840 mg loading dose followed by 420 mg every 3 weeks) was administered with the first paclitaxel cycle for patients with human epidermal growth factor receptor 2 (HER 2)-positive disease. At the completion of paclitaxel, patients were then scheduled to undergo single-stage BCT using MIB-PBI. Trastuzumab and Pertuzumab were administered every 3 weeks to complete the one-year duration.

Study population and outcome assessment

In the COMBAT-NEO study, the primary outcome was early AEs, and the secondary outcomes were late AEs, ipsilateral breast tumor recurrence (IBTR), and long-term cosmetic outcome (UMIN000026976). Early and late AEs were prospectively assessed at the completion of brachytherapy and in one month, with a follow-up every 3 to 4 months until 60 months and then every 12 months. In this study, physician-assessed AEs including higher grade skin toxicity, hemorrhage, symptomatic seroma, and breast infection were evaluated as clinically significant complications.[20] Grade 3 or more skin toxicity using the Common Terminology Criteria for Adverse Events (CTCAE, version 4.0) was defined as a higher-grade skin toxicity.[21] Postoperative hemorrhage was defined as any surgical procedures for hemostasis at the time of catheter removal. The definition of symptomatic seroma was one that requires multiple aspirations or leads to temporary drainage of the content from the wound. Breast infection was considered to be a surgical site infection (SSI) as defined by the Centers for Disease Control and Prevention National Nosocomial Infections Surveillance System criteria, including purulent drainage from the incision, organisms isolated from an aseptically obtained culture, and wound dehiscence.[22] Early AEs were defined as those occurring 3 months from the date of surgery, and those occurring later were defined as late AEs.

The evaluation of locoregional recurrence was performed using mammography and contrast-enhanced breast MRI every year. All locoregional, distant failure, and survival outcomes were evaluated on the date of the diagnosis. Bilateral tumors treated with MIB-PBI were counted as representing two patients. IBTR was divided into marginal miss and elsewhere failure, depending on the distance between the original tumor site and the recurrence site.[23]

All AEs and clinical outcomes were reported to the central office of Tokushukai Group Ethical Committee at 1, 3, 12 months, and every 12 months thereafter until 60 months following entry. In this preliminary report, the AEs and tumor control efficacy in patients undergoing MBI-PBI after NACT were compared with those in patients receiving MIB-PBI without NACT during the same period.

Statistical analysis

To estimate the proportion of complications over time and to compare complications among NACT, ACT and no-CT groups, contingency table analyses were performed. Differences between continuous variables and proportions were analyzed with ANOVA and Fisher's exact test, respectively. The Kaplan–Meier estimate was performed to evaluate the likelihood for IBTR. All p-values less than 0.05 were considered to be statistically significant. The analyses were conducted using SPSS software, version 27 (IBM SPSS Statistics for Windows, Armonk, NY).

Results

Patients and tumor characteristics and treatment variables

Between April 2017 and February 2020, 13 patients were received MIB-PBI after NACT. The clinical characteristics of all patients are shown in Table 1. In the NACT cohort, 12 patients (92.3%) received anthracycline and taxane-based therapy and 5 patients (38.5%) received anti-Her2 therapies. The medium time interval between the last dose of NAC and the surgery was 11 days (interquartile range [IQR], 8 – 17.5). There were 4 patients (30.8%) who achieved pathological complete response (pCR) and no patients were reported to be marginally positive (0%). During the same period of time, a total of 265 patients consequently received perioperative MIB-PBI including 13 NACT (4.9%), 68 ACT (25.7%), and 184 no-CT (69.4%). Table 2 summarizes patient and tumor characteristics, and treatment variables. At the time of this interim analysis, the median follow-up time was 30.0 months (IQR: 21.9 – 37.8), and all patients were followed up for at least 12 months. The median patient age and the average pathologic tumor size were 59.0 years (IQR: 49.0 – 69.0) and 10.0 mm (IQR: 6.0 – 15.0), respectively. Dosimetric valuables are shown in Table 3. The median volumes of the cavity and CTV equivalent to PTV were 11.4 cm^3 (IQR, 7.9 – 17.1) and 34.9 cm^3 (IQR, 21.5 – 48.3), respectively. The medium numbers of catheters and planes were 5 (IQR, 4 – 7) and 2 (IQR, 1 – 2), respectively. The target coverage of the protocol was achieved for all patients. Maximum fractional dose to the skin and the chest wall were 2.7 Gy (IQR, 2.5 – 2.9) and 2.4 Gy (IQR, 1.8 – 2.9), respectively.

Early adverse events

Physician-assessed AEs are summarized in Table 4. During the follow-up in the first 3 months, two grade ≥3 skin toxicities (0.8%), two hemorrhages (0.8%), six symptomatic seromas (2.3%), and three

Table 1. Clinical characteristics of 13 patients undergoing MIB-PBI after NACT

Age, years	Pretreatment clinical stage	Baseline IHC	Type of NACT	Axillary surgery	Pathological stage	Additional radiotherapy
45	cT1N1	ER+HER2-	AC-P	Dissection	ypT0N0	—
52	cT2N0	ER+HER2-	AC-P	SNB	ypTisN0	—
66	cT1N1	ER+HER2-	AC-P	Dissection	ypT1N0	—
50	cT2N1	ER+HER2+	AC-P+Tr	Dissection	ypT1N1	WBI
71	cT2N1	ER+HER2-	AC-P	Dissection	ypT1N1	WBI
41	cT2N1	ER-HER2-	AC-P	Dissection	ypT1miN0	—
63	cT2N0	ER-HER2+	D+Tr+Per	SNB	ypT1N0	—
63	cT2N1	ER+HER2+	AC-P+Tr	Dissection	ypT1N1	WBI
74	cT2N1	ER-HER2+	AC-P+Tr+Per	Dissection	ypTisN0	—
48	cT2N0	ER-HER2-	AC-P	SNB	ypTisN0	—
40	cT2N0	ER-HER2-	AC-P	SNB	ypT1N0	—
72	cT1N0	ER+HER2-	AC-P	SNB	ypT1N0	—
50	cT2N1	ER+HER2+	AC-P+Tr+Per	Dissection	ypT1N1	WBI

Abbreviations: NACT; neoadjuvant chemotherapy, IHC; immunohistochemistry, ER; estrogen receptor, HER2; human epidermal growth factor receptor 2, AC; adriamycin and cyclophosphamide, P; paclitaxel, DOC; docetaxel, Tr; trastuzumab, Per; pertuzumab, SNB; sentinel-node biopsy, WBI; whole-breast irradiation

Table 2. Patient and tumor characteristics receiving MIB-PBI among three different systemic treatment cohorts

Variables	NACT (n = 13)	ACT (n = 68)	no-CT (n = 184)	P
Median follow-up, months	33.6 (22.8–37.2)	29.5 (22.6–38.3)	30.1 (21.6–37.4)	0.96
Median age, years	52.0 (47.3–67.3)	62.0 (53.5–69.0)	58.0 (48.0–69.5)	0.54
*Median invasive diameter, mm	10.0 (1.5–14.5)	15.0 (10.0–20.0)	10.0 (4.0–15.0)	0.27
Margin status				
Negative/close	13 (100)	65 (95.6)	168 (91.3)	0.30
Positive	0 (0)	3 (4.4)	16 (8.7)	
**Lymph node status				
Negative/micrometastasis	5 (38.5)	64 (94.1)	181 (98.4)	<0.0001
Positive	8 (61.5)	4 (5.9)	3 (1.6)	
Axillary surgery				
SNB/no surgery	5 (38.5)	66 (97.1)	182 (98.9)	<0.0001
Axillary dissection	8 (61.5)	2 (2.9)	2 (1.1)	
Additional WBI				
Yes	4 (30.8)	1 (1.5)	1 (0.5)	<0.0001
No	9 (69.2)	67 (98.5)	183 (99.5)	
Adjuvant endocrine therapy				
Yes	9 (69.2)	45 (66.2)	171 (92.9)	<0.0001
No	4 (30.8)	23 (33.8)	13 (7.1)	
(Neo-) adjuvant chemotherapy				
Anthracyclines or taxanes	1 (7.7)	50 (73.5)	—	<0.0001
Anthracyclines and taxanes	12 (92.3)	18 (26.5)		
Anti-Her2 therapy				
Yes	5 (38.5)	26 (38.2)	—	0.99
No	8 (61.5)	42 (61.8)		

*Assessed for invasive tumor only. **Assessed by axillary surgery only. Abbreviations: NACT; neoadjuvant chemotherapy, ACT; adjuvant chemotherapy, CT; chemotherapy, SNB; sentinel-node biopsy, WBI; whole-breast irradiation, HER2; human epidermal growth factor receptor 2 Continuous variables are reported as medians (interquartile ranges). Categorical variables are reported as numbers (%).

Table 3. Dosimetric variables of patients receiving MIB-PBI among three systemic treatments

Variables	NACT (n = 13)	ACT (n = 68)	no-CT (n = 184)	P
Cavity volume, cm^3	12.5 (8.3–19.6)	13.0 (9.3–17.4)	11.2 (7.6–16.1)	0.65
PTV, cm^3	40.3 (15.8–61.7)	43.2 (27.1–52.2)	31.7 (21.0–46.0)	0.37
V100, cm^3	37.4 (12.2–63.3)	45.9 (28.4–56.3)	36.6 (24.3–53.3)	0.33
V150, cm^3	11.6 (5.5–28.0)	21.3 (11.8–29.6)	16.0 (9.7–26.2)	0.32
V200, cm^3	9.1 (5.2–12.5)	10.5 (6.2–15.3)	7.9 (5.7–14.6)	0.27
Maximum skin dose, Gy	2.6 (2.4–2.8)	2.7 (2.6–2.9)	2.7 (2.5–2.9)	0.90
Maximum chest wall dose, Gy	2.6 (1.4–3.7)	2.3 (1.6–2.9)	2.3 (1.8–2.9)	0.75

Abbreviations: NACT; neoadjuvant chemotherapy, ACT; adjuvant chemotherapy, CT; chemotherapy, PTV; planning target volume Continuous variables are reported as medians (interquartile ranges).

Table 4. Early and late adverse events receiving MIB-PBI among three different systemic treatment cohorts

	Onset	NACT (n = 13)	ACT (n = 68)	no-CT (n = 184)	Total (n = 265)	P
Skin toxicity	Early	0	2 (2.9)	0	2 (0.8)	—
	Late	0	0	0	0	
Hemorrhage	Early	0	0	2 (1.1)	2 (0.8)	—
	Late	0	0	0	0	
Symptomatic seroma	Early	0	1 (1.5)	5 (2.7)	6 (2.3)	—
	Late	1 (7.7)	1 (1.5)	0	2 (0.8)	
Surgical site infection	Early	0	0	3 (1.6)	3 (1.1)	—
	Late	0	1 (1.5)	1 (0.5)	2 (0.8)	
Total	—	1 (7.7)	5 (7.4)	11 (6.0)	17 (6.4)	0.91

Abbreviations: NACT; neoadjuvant chemotherapy, ACT; adjuvant chemotherapy, CT; chemotherapy
Categorical variables are reported as number (%).

SSIs (1.1%) were observed in the entire cohort. The cases of high-grade skin toxicities occurred as severe dermatitis on the area of radiation exposure with the first TC dose which could be diagnosed as a radiation recall reaction. The incidence of early AEs was observed in 10 ACT patients (5.4%) and three no-CT patients (4.4%). There were no clinically significant complications during the first 3 months in the NACT patients (0%).

Late and overall adverse events

After the 3 month follow-up, one symptomatic seroma each in the NACT (7.7%) and ACT (1.5%) patients and one SSIs each in the ACT (1.5%) and no-CT (0.5%) patients were observed. A rib fracture, telangiectasias, and other frequently reported major toxicities did not develop. Therefore, there were two grade ≥3 skin toxicities (0.8%), two hemorrhages (0.8%), eight symptomatic seromas (3.0%), and five SSIs (1.9%) observed in the entire cohort at all time points. The distribution of those adverse events had no significant coherence among three different systemic treatment cohorts (p = 0.91).

Tumor control outcomes

Overall, three IBTRs (1.1%) and one contralateral breast tumor were observed in the no-CT cohort. Both of the cases with IBTR occurred as a recurrence elsewhere. Based on a 2-year actual analysis of NACT, ACT, and no-CT patients, IBTR-free survival rates were 100%, 100%, and 98.8%, respectively. Because neither regional nor distant recurrences developed, breast cancer specific survival rate was 100%. One patient receiving NACT died from gastric cancer 24.2 months after MIB-PBI.

Discussion

NACT has been implemented in a multidisciplinary local treatment for early breast cancer. Although this interim report was based on a retrospective analysis with a small sample size and a short follow-up period, single-stage BCT with MIB-PBI following NACT did not demonstrate any early AEs, as well as any additional negative impact on wound complications and locoregional recurrences.

NACT was originally performed in patients with inoperable locally advanced disease for surgery and has been incorporated into operable disease in order to undergo BCT because of downsizing. According to the recent advances in systemic therapies, NACT has been performed not only to widen availability of BCT but also to investigate the pathological reaction to consider additional systemic treatment. For patients with residual disease in the breast after NACT (non-pCR), additional ACT using capecitabine and trastuzumab emtansine (T-DM1) have been considered for patients with high-risk luminal and triple-negative breast cancer, and HER2-positive disease, respectively.[11,12] The introduction of an immune-checkpoint inhibitor into NACT has also been considered for patients with triple-negative breast cancer to improve outcomes.[24] Those with increasing NACT use with extra AE were investigated because the cytotoxic agent may have a negative impact on the surgical wound recovery. However, evidence showing no extra risk of surgical complications and IBTR in selected patients has been reported.[15]

A deescalating local treatment needs to be considered for patients previously receiving NACT. For example, the ongoing RESPONDER trial aims to develop a precise approach for the assessment of pCR using a vacuum-assisted biopsy without surgical management following NACT.[25] PBI should be carefully considered after NACT as well. With various techniques and fractionation regimens available for PBI, efficacy of tumor control, AEs, and cosmesis can be obtained by adequate patient selection, technique, and dose delivery.[26] Although partial-breast brachytherapy was widely available with the longest follow-up, unique side effects, such as symptomatic seroma and breast infection from indwelling catheters and a higher gradient radiation dose may be observed. In the registry of partial-breast brachytherapy with an intracavitary device, 13% and 8.2% of symptomatic seroma and breast infection, respectively, were identified.[27] In our

series, there were eight (3.0%) and five (1.9%) patients who experienced symptomatic seroma and SSI, respectively. The low rate of infectious complications may in part be reflective of the prophylactic use of antibiotics, the reduced total time of indwelling brachytherapy catheter, and the utilization of the moving incision technique. Since NACT may defer wound healing, the risk for wound complications may increase. Similarly, because radiotherapy was started before wound recovery, perioperative PBI may be a concern. However, the incidence rate of the AEs in the NACT cohort was acceptable in our series.

There are some limitations to this study that should be noted. We acknowledge that this is an interim report based on a small number of patients and a short follow-up period. The data from the follow-up period was only sufficient to evaluate the early adverse event. Potential benefit of NACT for patients with small tumor has not been widely accepted, which may result in slow patient accrual. Second, the efficacy of PBI after NACT was based on a retrospective comparison to ACT and no-CT patients with different backgrounds. Finally, the generalizability of these results is limited to a single-institute with specific techniques. However, this study is very unique, and no other reports investigating the efficacy of PBI after NACT exists, and preliminary results support this study. We expect to be able to report on the safety and the possible efficacy of single-stage BCT using MIB-PBI at the completion of our trial.

Conflict of Interest

The authors declare that they have no conflict of interests.

Acknowledgments

The authors would like to thank Enago (www.enago.jp) for the English language review. The authors declare no conflicts of interest in association with the present study

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