Research article

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Non-pegylated liposomal doxorubicin plus cyclophosphamide as first-line therapy in elderly women with HER2 negative metastatic breast cancer

S.I.S. Fattoruso[4], R. De Luca[1], A. Grassadonia[2], S. Evola[3], A. Salvato[4], R. Addeo[4], G. Cicero[1]

[1]Department of Surgical, Oncological and Oral Sciences, Section of Medical Oncology, University of Palermo (Pa), Italy; [2]Department of Medical, Oral and Biotechnological Sciences, Gabriele D'Annunzio University of Chieti, Italy; [3]Cardiology Unit, University Hospital "P. Giaccone" (Pa), Italy; [4] Oncology Unit, ASL Napoli2 NORD, Frattamaggiore (Na), Italy

Abstract

Background. The use of anthracyclines in metastatic breast cancer (MBC) is limited by cumulative dose-dependent cardiotoxicity mostly in elderly women with comorbidities. The aim of this observational retrospective study was to evaluate the efficacy of non-pegylated liposomal doxorubicin (Myocet®) and cyclophosphamide in elderly women as HER2 negative first-line MBC treatment.

Methods. 84 elderly women >70 years of age (median age 78 years) with MBC HER2 negative were enrolled. Performance Status in 58 patients was ECOG-0 and in 26 patients was ECOG-1.

Results. The drug was well tolerated, with overall response rates were >40%, median overall survival was 16.2 months (95%CI:14.6-18.8) and median progression free survival was 5.8 months (95%CI:4.4-8.6). Hematologic toxicity with neutropenia was the most frequent adverse event , but the treatment was well tolerated maintained a manageable cardiotoxicity.

Conclusion. Non-pegylated liposomal doxorubicin may represent a valid therapeutic option in first-line for elderly patients with HER/2 negative MBC improving survival, anti-tumor response rate and decreases cardiotoxicity. ***Clin Ter 2022; 173 (2):121-127 doi: 10.7417/CT.2022.2405***

Key words: *Ca 15-3, Cyclophosphamide, Elderly woman, Metastatic breast cancer, Non-pegylated liposomal doxorubicin, Quality of life*

Introduction

Breast cancer (BC) is the most frequent malignant disease in women and represents the leading cause of death among women in all countries. The 22% of new BC diagnoses and 14% of BC deaths occur in elderly women ≥70 years old. Despite the high incidence of metastatic breast cancer (MBC) in old women, clinical studies examining specifically this population, unfortunately, remain a few number (1-2). Anthracyclines are the most widely used cytotoxic agents in MBC and their use, alone or in combination with taxanes , has improved survival curves and overall response rates (ORR) (3-4). Anthracyclines, such as doxorubicin, play a central role in the management of every BC stage , particularly in the early stages. The wide use of them in early stages limit their use in metastatic setting due to the cardiotoxicity gained by these drugs, represented by potentially fatal congestive heart failure, and to the cumulative life-long dose defined for each of them, expecially for doxorubicine .The cardiotoxicity is assessed, not only clinically, but also by measuring the left ventricular ejection fraction (LVEF), with baseline echocardiography and then every three months (5). The mechanism of anthracycline cardiotoxicity consists in the induction of damage to mitochondrial DNA, in the production of free radicals and in the interference in metabolism of the myocardium with consequent irreversible reduction of the ventricular function of the myocardium and therefore heart failure (6-7). In order to limit anthracycline-related cardiotoxicity, a non-pegylated liposomal doxorubicin (Myocet®) have been developed. This has got a significantly lower cardiotoxicity than doxorubicin, but a similar antitumor efficacy (8-9). Non-pegylated liposomal doxorubicin is a doxorubicin complexed with citrate ions, encapsulated in a liposome, without cardiotoxic effect because it does not accumulate in the heart tissue. At the same time it has got the same anticancer efficacy as doxorubicin and it seems to easily pass through the damaged capillaries of tumor tissues (10). Non-pegylated liposomal doxorubicin mechanism of action is important to preserve a good left ventricular function. Asymptomatic and symptomatic cardiotoxicity occurs for conventional anthracyclines for cumulative doses between 360 and 480 mg/m^2 while for non-pegylated liposomal doxorubicin 1260 mg/m^2. Non-pegylated liposomal doxorubicin anti-cancer efficacy and improved cardiological tolerability have been demonstrated in three randomized Phase II and III studies (11,12, 13). In the Phase III study Chan et al. compared non-pegylated liposomal doxorubicin plus cyclophosphamide (MC) vs epirubicin and cyclophosp-

Correspondence: Prof. Giuseppe Cicero, MD, PhD, Department of Surgical, Oncological and Oral Sciences, University of Palermo Via del Vespro, 129, 90127 Palermo, Italy. Tel: +3909126554406. Email address*:* giuseppe.cicero@unipa.it

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hamide (EC) in first-line treatment in patients with MBC. At a median follow-up of 21 months there were no differences in ORR (46% vs 39% respectively) and overall survival (OS) (18.3 vs 16.0 months) while the time to progression (TTP) was in favor of non-pegylated liposomal doxorubicin (7.7 vs 5.6 months) with less cardiotoxicity (13). This observational retrospective study was conducted to evaluate the safety, the therapeutic efficacy and the increased cardiological tolerability of non-pegylated liposomal doxorubicin in elderly patients with first-line MBC HER2 negative. The ORR, OS and progression free survival (PFS) were primary endpoints ; while tolerability, reduction of carcinoembryonic antigen 15.3 (Ca 15.3) levels (before and after treatment), and quality of life (QoL) were secondary endpoints. The study was approved by ethic committee and was conducted in accordance with Helsinki Declaration and good clinical practice guidelines. All patients gave written informed consent to treatment. All clinical information for each eligible patient were retrospectively collected employing an anonymous electronic database.

Materials and methods

Patients

In this observational retrospective study, between march 2014 and June 2018, we enrolled 84 elderly patients ≥70 years old. All patients had to meet the following inclusion criteria: 1) histologically or cytologically confirmed HER2 negative MBC with measurable or evaluable disease; 2) unresectable stage IV carcinoma pretreated with conventional therapies for at least 1 year; 3) performance status between 0 and 1 in according to Eastern Cooperative Oncology Group (ECOG); 4) regular heart function with LVEF >50% and electrocardiogram (ECG) with sinus rhythm; 5) adequate bone marrow, renal and hepatic function ; 6) clinical or radiological evidence of metastatic measurable disease by spiral computer tomography (CT) scan or magnetic resonance imaging (MRI) scan, in accordance with Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (14) with a number lesions ≥1; 7) patients with asymptomatic central nervous system metastases and with surgery or radiotherapy no more than three months. Were excluded from the study: 1) patients hypersensitive to non-pegylated liposomal doxorubicin or cyclophosphamide and its excipients or other components of formulation; 2) previous adjuvant and/or neoadjuvant chemotherapy with achievement of maximum permitted cumulative dosage of adriamycin equal to 450 mg/m^2 and epirubicin equal to 900 mg/m^2; 3) patients with diagnosis of other malignancies, with exception of skin basal cell carcinoma adequately treated; 4) patients with symptomatic brain metastases; 5) patients presenting severe co-morbidities not adequately controlled by other ongoing therapies (e.g. liver disease, diabetes, infections, heart disease, etc.).

Modality of administration

Non-pegylated liposomal doxorubicin 60 mg/m^2 in combination with cyclophosphamide 600 mg/m^2 were somministered with intravenous injection on day 1 every 21 days. In addition, during entire treatment period, the patient was advised to maintain adequate hydration in order to prevent complications such as kidney failure. Cardiological function was assessed at beginning and every three months. According to clinical practice procedures, the therapy was postponed for up to 2 weeks, if neutrophil count was <1.5×10^9/L, if platelet count was <100×10^9/L, if hemoglobin level was <8.5 g/dl, if bilirubin and/or transaminase levels were >1.5×ULN. In case of neutropenia (G3-G4) G-CSF was administered in advance, under skin, in case of significant anemia, (G3-G4) blood transfusions were performed, in less severe cases erythropoietin vials were performed under skin, and finally in case of thrombocytopenia (G3-G4) were administered infusions of platelet, intravenously. In the event of stable disease or in presence of an important (partial or complete) response, each patient received treatment up to progression or maximum tolerated dose of anthracyclines or toxicity. Progressing patients were assigned to begin a new treatment. Concomitant treatments that did not interfere with MC treatment, including use of bisphosphonates were administered.

Evaluation of the response and toxicity

Evaluation of response rates in terms of stability or reduction of measurable lesions, according to RECIST criteria, was conducted at begin of treatment and every three months until disease progression. ECG and echocardiogram, to evaluate LVEF, were performed before start the treatment then every three cycles or at physician discretion. CT scan was always performed before begin of treatment, and on average every three months or in coincidence with presumed progression. Total body bone scan was performed before treatment and on physician discretion and clinical need every 6 or 12 months. The positron emission tomography (PET) was performed in selected cases on physician discretion. In case of brain metastases, a MRI scan was performed every 6-12 weeks. Baseline laboratory assessments were done 14 days before randomization, and assessments were done throughout treatment phase. Drug-related toxicities (DRT) were graded according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Patients were withdrew from the study for cardiac toxicity, defined as a decrease in resting LVEF of >20 units from baseline to a final value of >50%, or a decrease of >10 units from baseline to <50%, or evidence CHF clinic. The treatment was continued until clinical benefit was observed or until treatment was no longer tolerated. Furthermore, we evaluated percentage of response, in terms of Ca15.3 reduction, comparing the mean scores of serum levels, before and after treatment.

Quality of Life value

QoL was routinely assessed to all patients, at treatment start and at first follow-up (three months), the questionnaire was administered by psycho-oncologist. The European Organization for Research and Treatment of Cancer (EORTC QLQ-C30) questionnaire (15) is composed to five functional scales (physical, role, cognitive, emotional, social), three symptom scales (fatigue, pain, nausea and vomiting), a single

global health status scale, and six single items (dyspnea, loss of appetite, insomnia, constipation, diarrhea and financial impact). A higher score represents high response level, but a higher score for symptom scale/item represents high level of symptomatology.

Statistical analysis

OS and PFS curves were estimated by using the Kaplan-Meier method. Bravais-Pearson (r) linear correlation index was used to quantify the relation between PFS and QoL, with 95% confidence interval (CI). The statistical significance was defined as a P *value* of less than 0.05. Last follow-up in December 2019. Statistical analysis was performed using Statistical Package for Social Science (SPSS) software, version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Patients' characteristic

Median age of patients was 78 years (range 70-84 years). Adjuvant chemotherapy was administered to all patients. Forty-eight patients had positive estrogen and progesterone receptors; thirty-two patients had negative estrogen and progesterone receptors. Performance Status was ECOG-0 for 58 patients and ECOG- 1 in 26 patients. No episodes of symptomatic cardiotoxicity and no clinical CHF was observed. LVEF was determined by two-dimensional M-mode echocardiography and cardiotoxicity was measured as the decrease in resting LVEF of >20 units from baseline to a final value >50%, or decrease of >10 units, from baseline to <50 %, with clinic evidence of CHF. Only two patients had asymptomatic reductions in LVEF with cumulative doses between 400 and 499 mg/m^2 and four patients with 500-599 mg/m^2. Adjuvant therapies performed by patients were: CMF (cyclophosphamide-methotrexate-fluorouracil) 14%; EC (epirubicin-cyclophosphamide) 22%; EC→T (paclitaxel) 48%; TC (docetaxel - cyclophosphamide) 16% and cyclin inhibitors 4%. The sites of metastasis were: bone in 54 patients; liver in 6 patients; lung in 8 patients; lymph node in 28 patients (Tab. 1). All patients were in postmenopausal status and hormone receptor positive received hormone therapy. Seven patients following reduction in size and number of the liver metastases performed thermal ablation.

Table 1. Baseline demographic and clinical characteristics (n. 84)

Characteristics	Patients
Mean age [range]	78 [70-82]
ECOG performance status	
0	58
1	26
Histology	
ER and PR (+)	48
ER and PR (-)	32
Median Ca 15.3 level [range], ng/mL < 35 cut off	160 [90-307]
Metastatic site	
Liver	6
Lung	8
Bone	54
Lymph nodes	28

Note: ECOG= Eastern Cooperative Oncology Group; ER= estrogen receptors; PR= progesterone receptors.

ORR analysis

Our analysis showed that MC treatment was well tolerated in all patients, with ORR (RP+RC) of 42% and with a good level of disease control rate (DCR: RC+PR+SD) >50%. Treatment response to patients was: 4% had a complete response (RC), 38% had a partial response (PR), 42% had disease stabilization (SD), 16% had disease progression (PD). The treatment was well tolerated and led to a good level of disease control (RC+PR+SD) >50% (Tab. 2). The median duration of response time was 5.8 months (95% CI 4.6-6,8) with a significant impact on QoL. MC treatment determined an ORR significantly greater in patients with liver and lung metastasis.

OS and PFS analysis

Interim survival analysis showed an OS value of 16.2 months (95% CI 14.6-18.8), (Fig. 1). Median PFS was 5.8 months (95% CI 4.4-8.6), (Fig. 2). The PFS is associated positively with QoL, in fact, by means of the Bravais-Pearson index, a modest correlation between these two variables has been demonstrated with a HR (95% CI) value of 0.59 (0.27-0.89), p=0.008 (Tab.3).

Table 2. Overall Response Rate (n. 84)

Best response	**Investigator assessment (%)**
Complete response	(4)
Partial response	(38)
Stable response	(42)
Progressive response	(16)
Overall response rate (CR+PR)	(42)
Clinical benefit rate (CR+PR+SD)	(84)

Note: CR = complete response; PR = partial response; SD = stable response.

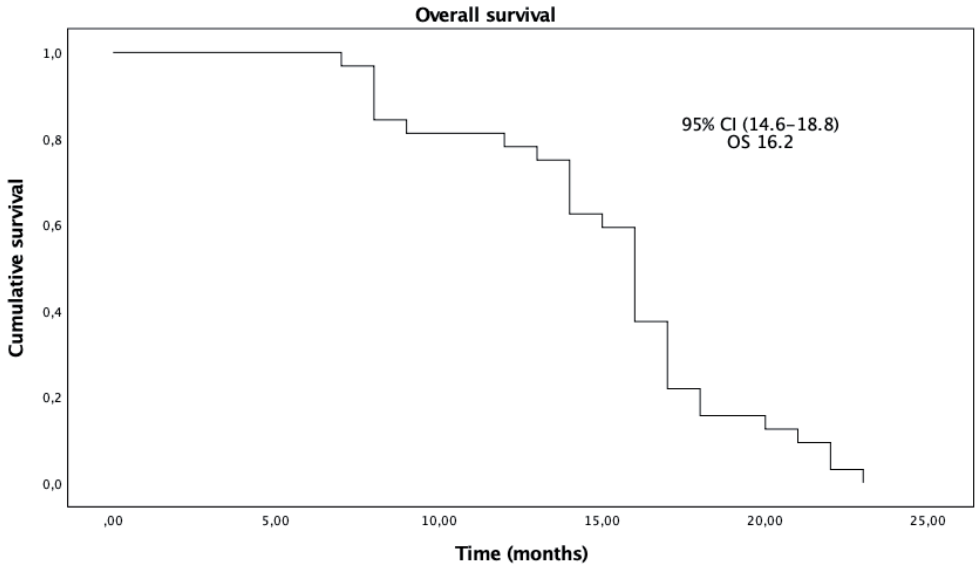

Fig.1. Kaplan-Meier plot of median Overall Survival (OS) (n. 84)

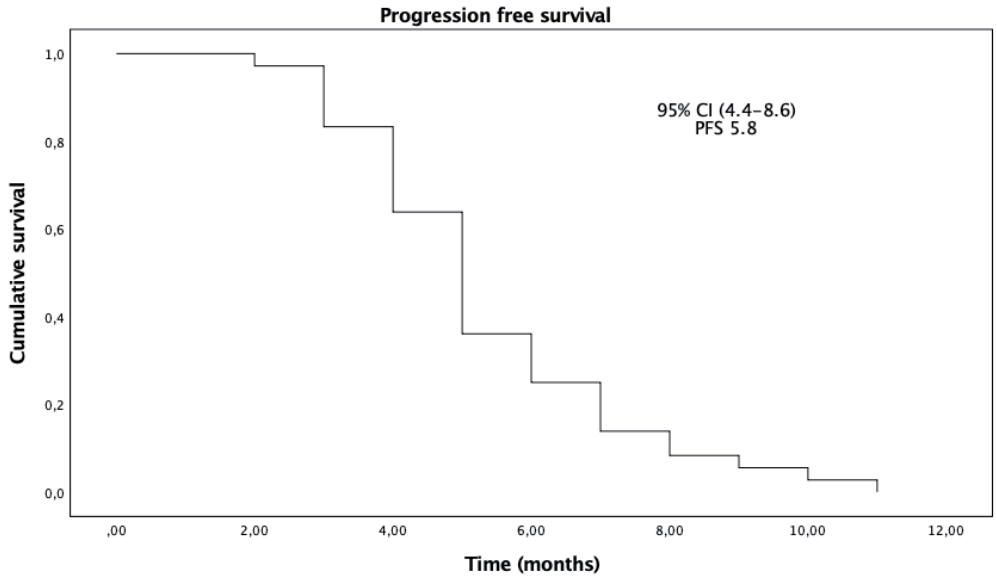

Fig. 2. Kaplan-Meier plot of Progression Free Survival (PFS) (n. 84)

Table 3. Pearson's correlation among QoL and PFS (n. 84)

	QoL	PFS	p
QoL	1	-0.59**	0,008
PFS	-0.59**	1	0,008

Note: PFS= Progression Free Survival; QoL= Quality of Life; **p < 0.01

Quality of Life analysis

QoL measured with EORTC QoL-C30 questionnaire (16) showed a score of 45 (0-100) in global health status scale. The QoL showed an improvement with the treatment with a score of 56 (0-100). Scores on the functional scales indicate that QoL was sufficient almost il all patients . An improvement in QoL was also identified with a reduction in pain symptoms.

Ca 15.3 reduction

During treatment with MC, Ca15.3 levels partially decreased in forty-two patients (Tab. 4). In the other patients,

Table 4. The average scores Ca 15.3 ante- and post- treatment, with the Paired Samples Test (n. 84)

	Mean	SD	t		p
Ca 15.3 Pre-treatment	160	4.17	7.96		0.006
Ca 15.3 Post-treatment	50	4,46			

the increase in Ca15.3 values corresponded to a progression of neoplastic disease.

Tolerability

Treatment-related toxicity was of low grade and adverse events were evaluated after each course of therapy and reported in line with CTCAE version 4.0. No patient died from treatment-related adverse events. All patients continued treatment until progression or unacceptable toxicity. Hematological toxicity was a major complication managed with dose adjustment or reduction. Among the hematological toxicities, neutropenia was the most frequent and most serious adverse event. Neutropenia occurred G3-G4 in 22 patients (26%) and required use of G-CSF as prophylaxis. 7 patients (8%) developed febrile neutropenia (G3-G4) requiring use of G-CSF and antibiotics with dose reduction to 50 mg/m^2. G3-G4 thrombocytopenia developed in 5 patients (6%) and required use of corticosteroids. 11 patients (9%) developed G3 anemia required subcutaneous erythropoietin administration. All G4 toxicity were managed by dose modifications. The dose was reduced in six patients (50 mg/m^2) and was postponed in four patients. Due to deteriorating clinical condition, older age and comorbidities, one patient discontinued treatment after three infusions. Only one patient received 80% of MC from the first cycle due to clinical conditions. Other more common side effects were: alopecia G2-G3; nausea and vomiting 12%; asthenia 18% G2-G3; 8% stomatitis and mucositis G2-G3. (Tab. 5). The therapy-related adverse reactions were resolved with safety guidelines application.

Discussion

Anthracyclines are key drugs in the treatment of MBC and are capable of inducing significant benefits on PFS and OS with a good ORR >40% (16). In recent years, an increasing proportion of patients have been exposed to adjuvant anthracyclines with concomitant reduction in their use in advanced stages due to cumulative cardiotoxicity which is fatal in more than 5% of patients when with a cumulative dose of 450 mg^2 (17-18). Elderly patients are more likely to have fragile heart function due to often silent coronary atherosclerosis, hypertension, diabetes, anemia and other cardiovascular diseases than under conditions of cardiac stress, such as cardiotoxic antiblastic chemotherapy, can progressively progress to severe heart failure (19-20). Comparative studies with non-pegylated liposomal doxorubicin (11) have not only demonstrated a valid and effective antitumor activity but a lower impact on cardiotoxicity, which improves patients' perspective on the duration of ongoing treatment and on the possibility of being suitable for subsequent therapeutic lines (21-22, 23). In this retrospective observational study, we showed that MC combination could be a valid and effective first-line treatment for elderly patients with MBC, because reduces cardiac risks while maintaining good anticancer efficacy, with a median OS of 16.2 months, a median PFS of 5.8 months, a good level of disease control >50% and with a good safety profile. In this

Table 5. Adverse events graded according CTCAE, Version 4.0 (n. 84)

Adverse Events	All Grades (%)	Grade 3-4 (%)
Hematological		
Anemia	12	9
Neutropenia	31	26
Thrombocytopenia	26	6
Febrile neutropenia	-	8
Non-hematological		
Nauvcbsea	32	14
Vomiting	26	12
Fatigue	38	18
Alopecia	88	62
Stomatitis/mucositis	21	12
Bone pain	-	-

Note: CTCAE = Common Terminology Criteria for Adverse Events.

study, geriatric assessment was only performed in thirty-two patients because the experienced geriatrician was not always available in our healthcare facility (24-25). This study could confirm that age alone should not preclude the use of MC in elderly patients also in consideration of lower cardiotoxicity that has contributed to maintaining a good QoL. MC has showed an efficacy equivalent to that of conventional anthracyclines with a lower cardiological and hematological toxicity. Non-pegylated liposomal doxorubicin with cyclophosphamide showed an increase in survival curves in our study with a good response rate and a manageable toxicity profile. These results, although promising and in line with the data of the scientific literature (26-27) are related to a retrospective analysis, this represents a limitation that needs confirmation with prospective randomized studies focused only on elderly patients, moreover, also QoL assessment confirms the manageability of treatment even in patients with advanced age (28).

*(REVISIONE) The safety profile of Non peghilated liposomal doxorubicin makes its employment encouraging also in combination with taxane and monoclonal antibodies in different disease settings such as neoadjuvant and adjuvant ones, such as in GeparSixto study (NCT01426880) where patienst were scheduled to receive paclitaxel 80 mg/m2 plus nonpegylated liposomal doxorubicin (NPLD, MyocetVR) 20 mg/m2 , both administered q1w for 18 weeks. Patients with TNBC received additionally bevacizumab 15 mg/ kg q3w during all chemotherapy cycles. Patients with HER2-positive disease received trastuzumab 6 (loading dose 8) mg/kg intravenously q3w and continuously oral lapatinib 750 mg once per day. Patients were randomized to receive simultaneously carboplatin (PMCb) at 2.0 (reduced to 1.5 after accrual of 330 patients) area under curve (AUC) q1w for 18 weeks or no additional treatment (PM) [1]. Different studies demonstrated the efficacy and safety of liposomal doxorubicin used contemporary to trastuzumab or bevacizumab (29-34).

Trastuzumab in elderly patients already represents a standard of care (36-37).

Particularly in HERA trial trastuzumab was administered after epirubicin and no more congestive heart failure was demonstrated with the association of antracycline and trastuzumab .

Also in the metastatic setting, the HERCULES trial found that the combination of trastuzumab with epirubicin plus cyclophosphamide was feasible with manageable cardiotoxicity despite of escalating doses of epirubicin (60 and 90 mg/m2).

Considering that Myocet has got less cardiotoxicity than epirubicin , this make us sure it can be also preferable to epirubicin expecially in elderly women.

Furthermore bevacizumab has been studied and it demonstrated a good tolerability profile with no more cardiotoxicity. These data represents an optimal background for testing non peghilated liposomal doxorubicin in concomitant use or in sequence with monoclonal antibodies suc as trastuzumab, pertuzumab and bevacizumab in neoadjuvant, adjuvant e metastatic setting instead of classic doxorubicin or epirubicin. More clinical studies are required in this setting.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflicts of interest associated with this research.

Research involving human participants All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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