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ORIGINAL ARTICLE

An all-oral combination of metronomic cyclophosphamide plus capecitabine in patients with anthracycline- and taxane-pretreated metastatic breast cancer: a phase II study

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Abstract
Purpose Oral administration of cyclophosphamide (CTX) and capecitabine may have a greater potential for treatment of metastatic breast cancer (MBC) due to anti-angiogenesis resulting from the metronomic dosage and upregulation of thymidine phosphorylase by CTX. The purpose of this phase II study was to evaluate the efficacy and safety profile of an all-oral combination of metronomic CTX plus capecitabine for women with anthracycline- and taxane-pretreated MBC.
Method In this prospective single-center, open-label, phase II trial, patients with measurable disease received oral metronomic CTX 65 mg/m^2 daily on days 1–14 plus capecitabine 1,000 mg/m^2 twice daily on days 1–14. The treatment was repeated every 3 weeks, and continued until disease progression, unacceptable toxicity or withdrawal of informed consent. The primary endpoint of the study was time to progression (TTP).
Results A total of 68 patients were enrolled and received 537 cycles of chemotherapy with a median of 8 cycles (range: 1–30 cycles) per patient. Sixty-six patients were evaluated for efficacy with all patients for toxicity. With a median follow-up time of 26 months, the median time to progression was 5.2 months (95% CI, 4.2–6.2 months), and the median overall survival was 16.9 months. The overall response rate was 30.3% (95% CI, 20–43%). Clinical benefit rate was 53.0% (95% CI, 38–62%). The doublet was well tolerable, with anorexia (7.5%), the only grade 3/4 adverse events occurring in more than 5% of patients. Grade 3 hand–foot syndrome was 4.4%.
Conclusion The all-oral combination of metronomic CTX plus capecitabine is an effective and convenient and well-tolerated regimen for MBC. (ClinicalTrials.gov number, NCT00589901).

Keywords Metronomic cyclophosphamide · Capecitabine · Metastatic breast cancer · Oral chemotherapy · Phase II

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Introduction

Despite advances in treatment of patients with metastatic breast cancer (MBC), prognosis remains poor and median survival is 2–3 years [1, 2]. Anthracycline and taxanes are effective agents in advanced breast cancer and prolong survival time, so they are generally considered as the most effective cytotoxic agents for the management of MBC. However, during the past 10 years, anthracyclines and taxanes have become mainstays in the adjuvant and neo-adjuvant settings, and approximately one third of patients fail to respond to first-line treatment with anthracycline or taxanes in MBC. Therefore, treating patients with anthracycline- and taxane-pretreated/resistant MBC represents a significant challenge to oncologists. Capecitabine, gemcitabine, vinorelbine, cisplatin or other agents are generally used at the physician's discretion to treat patients who have failed both anthracycline and taxanes.

Oral administration of anticancer drugs is a valuable medication route in patients with breast cancer. Oral administration of endocrine therapy and small molecular

targeting agents is widely used in the clinic. Published data have suggested that chemotherapeutic agents can be also taken orally with sound efficacy and good safety profile. The earliest trial using oral cyclophosphamide (CTX) showed that the response rate with the classical CMF including oral CTX was 48%, significantly higher than 29% with the intravenous CMF including intravenous CTX ($P = 0.003$). Median survival time also favored the classical CMF (17 vs. 12 months, $P = 0.016$), although response duration was similar at 11 months [3]. Capecitabine is another successful paradigm. Multiple clinical trials published from 1999 to the present have already demonstrated that capecitabine, either as a single agent or in combination with other agents, has an objective response rate (ORR) of 10–53.9%, median progression-free survival or time to progression of 3.4–8.1 months and median overall survival of 10–28 months in anthracycline- and taxane-pretreated and/or resistant MBC [4–24].

Anti-angiogenesis is a possible new-found mechanism involved in the antitumor efficacy of oral administration of anticancer drugs [25, 26]. Colleoni et al. reported that metronomic low-dose of CTX and methotrexate induces a drop in serum level of vascular endothelial growth factor (VEGF), and is effective and minimally toxic [26]. Daily low-dose/continuous capecitabine (825 mg/m^2 twice daily for 5 days a week) combined with neoadjuvant irradiation is also shown to reduce both serum VEGF and PDGF-BB (platelet-derived growth factor) levels in colorectal cancer patients [27].

Moreover, there may be a synergy between the two drugs due to the upregulation of thymidine phosphorylase (dThdPase) by CTX [28, 29]. Several other chemotherapeutic agents, like docetaxel, paclitaxel and mitomycin C can up-regulate intra-tumoral dThdPase and their combinations with capecitabine have translated into clinical benefits. Randomised clinical trials have already demonstrated that the combination of docetaxel with capecitabine significantly improves response rate, time to progression and overall survival compared with docetaxel alone in anthracycline-pretreated patients [30]. Paclitaxel in combination with capecitabine has been shown to have a comparable efficacy to the doublet of paclitaxel and epirubicin while used as first-line treatment for MBC [31].

In view of the potential synergy between the two drugs and their anti-angiogenesis mechanism, with favorable indexes of efficacy to toxicity, a clear rationale for the combination of CTX and capecitabine for MBC patients is thus established. A phase II study was conducted to evaluate the efficacy and safety of an all-oral combination of metronomic CTX plus capecitabine in patients with anthracycline- and taxane-pretreated MBC (ClinicalTrials.gov number, NCT00589901). CTX was determined at 65 mg/m^2 based on the phase I trial conducted by Ohno et al. This phase I trial which explored the dosage of the CTX plus capecitabine doublet for patients with MBC recommended that capecitabine 829 mg/m^2 and CTX 33 mg/m^2 twice daily on days 1–14 and repeated every 3 weeks is feasible and extremely well tolerated [32]. However, capecitabine at 829 mg/m^2 maybe too low thus 1 g/m^2 was used instead as a more favorable therapeutic index in metastatic breast cancer has been demonstrated [33].

Patients and methods

Eligible subjects

The study population included women (≥18 years of age) with a histologically or cytologically confirmation of the diagnosis of MBC diagnosis. All patients had at least one measurable disease according to RECIST 1.0 criteria, a life expectancy of no less than 3 months, previous treatment with an anthracycline and a taxane in the adjuvant and/or advanced disease setting. Anthracycline and taxane treatment could be administered concurrently or sequentially. Patients could have received up to four previous chemotherapy regimens in the advanced disease setting. Prior hormone therapy was permitted, as were surgery and radiation therapy, provided that they did not affect evaluation of measurable disease. In addition, patients were required to have Eastern Cooperative Oncology Group performance status of 0 or 1, and to have completed all prior chemotherapy and radiotherapy at least 4 weeks before study entry. Patients on bisphosphonate therapy for metastatic bone disease must have initiated therapy 3 months before study entry. All patients had adequate hematologic, hepatic, renal, and cardiac function, indicated by hemoglobin ≥ 10 g/dl, absolute neutrophil count ≥ 1.5×10^9/l, platelet count ≥ 100×10^9/l, total serum bilirubin ≤ 1.0 × upper normal limit (UNL), AST/ALT ≤ 2.5 × UNL, (≤5 × UNL in case of liver metastases), alkaline phosphatase ≤ 2.5 UNL (or ≤5 UNL for bone metastases) and creatinine clearance ≤ 1.0 × UNL. Her-2 positive patients who met the above criteria but couldn't afford trastuzumab due to ineligibility for medical insurance coverage were also enrolled in this study.

The main exclusion criteria were pretreatment with capecitabine or oral CTX, evidence of CNS metastasis, radiation to more than 25% of bone marrow, or uncontrolled intercurrent infection.

Written informed consent was obtained from all patients prior to enrollment. The study was approved by the Fudan University Cancer Hospital Ethic Committee for Clinical Investigation (approval number: 43-9).

Study design and treatment protocol

This was a single-arm, open-label, single-center, phase II study conducted between August 2006 and December 2008. The primary endpoint of the study was time to progression (TTP). Secondary endpoints included tumor response rate, overall survival (OS) and safety.

Patients received 21-day cycles of oral metronomic CTX 65 mg/m^2 daily and oral capecitabine 1,000 mg/m^2 twice daily on days 1–14 followed by a 7-day rest period. No prophylactic antiemetic medication, like a 5-HT3 receptor antagonist was permitted in the first cycle of chemotherapy. Treatment was continued until disease progression, unacceptable toxicity or patients' consent was withdrawn.

Because an oral capecitabine tablet in 150 mg is not available in China, actual given doses of capecitabine were 2,500, 3,000, 3,500 and 4,000 mg per day based on patient's body surface area of 1.25–1.37, 1.38–1.65, 1.66–1.99 and $\geq$2.0 m^2, respectively. An oral CTX tablet was dosed in 50 mg.

Dose modifications

Dose adjustments and/or treatment delays were made in the event of dose-limiting hematological or non-hematological toxicities. In patients experiencing adverse events of grade 2 or higher severity, the standard capecitabine dose modification scheme, as described in detail by Blumand and colleagues [4], was applied. The start of a new treatment cycle was delayed until treatment-related adverse events resolved to grade 0 or 1. Omitted capecitabine or CTX doses were not replaced or restored. If study treatment could not be started 2 weeks later than the predesignated date due to any toxicity, it had to be permanently discontinued. If the agents had to be permanently discontinued, the patient would go to the follow-up stage. Patients experiencing grade 3 or 4 neutropenia, with or without fever, were allowed to receive granulocyte colony-stimulating factor in subsequent cycles at the investigator's discretion.

Study assessments

Responses were assessed every two cycles. TTP was defined as the interval between treatment start and tumor progression, or death in patients with no evidence of disease progression. A complete response (CR) required a complete disappearance of all lesions, and a partial response (PR) required at least a 30% decrease of the sum of the longest diameters of target lesions. Both CR and PR had to be confirmed at least 4 weeks later. Stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease. Progressive disease (PD) was defined as at least a 20% increase in the sum of longest diameters of target lesions and/or the appearance of new lesions. Clinical benefit was defined as patients achieving CR, PR or SD, maintained for a minimum of 6 months. Overall survival was defined as the interval between the initiation of treatment and death.

Safety was evaluated in patients who received at least one dose of capecitabine and CTX. Adverse events were graded 1–4 according to the National Cancer Institute Common Toxicity Criteria (NCI CTC), version 3.0. Hand–foot syndrome was graded 1–3, as defined in previous capecitabine trials [4].

Statistical analysis

The estimation of the sample size was based on the ability to detect a clinically meaningful improvement in the primary end point. The median TTP for patients pretreated with taxane-based therapy who received oral capecitabine was 3.2 months [5]. An improvement of a median TTP to 5.0 months by the addition of metronomic CTX plus capecitabine was considered clinically significant. The study would have 80% power to detect a clinically meaningful improvement, with the use of an unstratified log-rank test, at a one-sided significance level of 5%. Taking into account the estimated rate of patient accrual and a 10% loss of the study, we estimated that we would have to enroll 63 patients.

TTP (the primary endpoint) analyses were performed on the evaluable population. Safety analyses were performed on the intention-to-treat population. Data of baseline characteristics of patients and tumors were analyzed by descriptive statistical methods. The Kaplan–Meier method was applied to TTP and overall survival. Overall response rate and clinical benefit rate (CR + PR + SD $\geq$ 6 months) were tabulated together with 95% confidence interval (CI).

Results

Patient characteristics

From August 2006 to December 2008, 68 patients were enrolled and their characteristics are listed in Table 1. All the patients had been exposed to anthracyclines and taxanes either as an adjuvant treatment or as treatment for relapse. Thirty-three patients had received containing 2-h 5-FU infusion in adjuvant setting. The enrolled patients had a median age of 50.7 years (range: 29–70). The median

Table 1 Baseline characteristics of patients

Characteristics	$N = 68$	%
Median age, years (Range)	50.7 (29–70)	
<65	60	88.2
≥65	8	11.8
Performance status at baseline (ECOG)		
0	43	63.2
1	25	36.8
Hormonal status		
ER or PR positive	37	54.4
ER and PR negative	30	44.1
ER and/or PR unknown	1	1.5
Her-2 status		
Positive	10	14.7
Negative	58	85.3
Number of metastatic sites		
1	18	26.5
2	21	30.9
>2	29	42.6
Sites of metastases		
Liver	27	39.7
Lung/pleura	31	45.6
Bone	35	51.4
Lymph/soft tissue	30	44.1
Number of previous chemotherapies for metastatic disease		
0	15	22.1
1	30	44.1
≥2	23	33.8
Prior chemotherapy		
Adjuvant	60	88.2
Anthracycline-based without taxanes	35	51.5
Anthracycline and taxanes	18	26.4
CMF	7	10.3
Metastatic disease		
Taxanes	35	51.5
Anthracycline and taxane	15	22.1
Vinorelbine	23	33.8
Gemcitabine	15	22.1
Cisplatin	12	17.6
Trastuzumab	2	2.9

body surface area was 1.60 m^2 (range: 1.35–1.98), 77.9% (53/68) patients were administered total daily dose 3,000 mg of capecitabine and 98.5% (67/68) patients were administered CTX 100 mg daily. The majority of the patients had visceral metastases, with 70% manifesting more than two metastatic sites. Forty-four percent of them had received one chemotherapy regimen for advanced disease, 33.8% had received two or more different chemotherapy regimens.

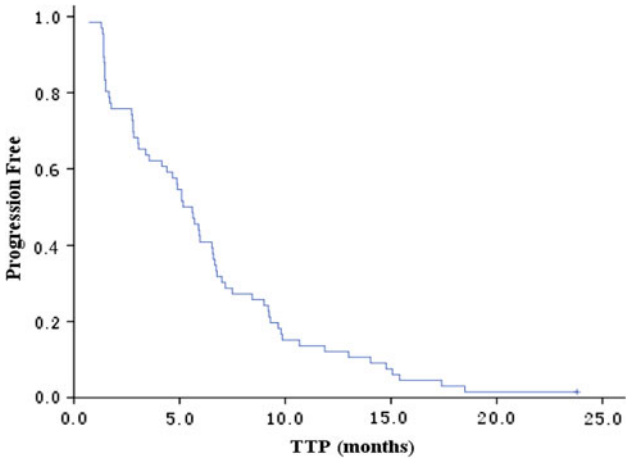

Fig. 1 Kaplan–Meier curve demonstrating the time to progression (TTP). The median TTP was 5.2 months (95% CI: 4.2–6.2)

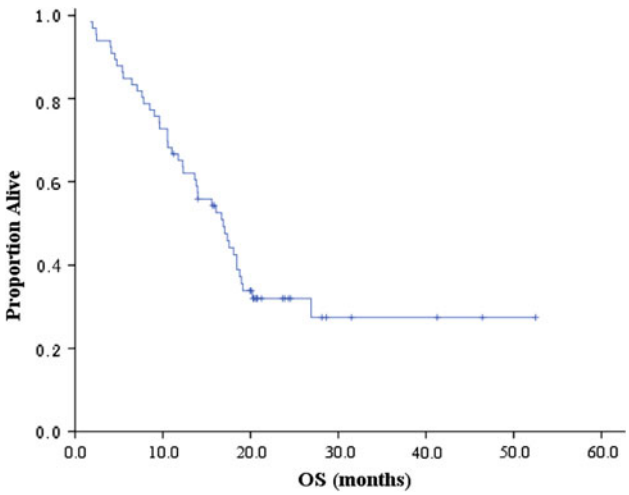

Fig. 2 Kaplan–Meier curve demonstrating the overall survival (OS). The median OS was 16.9 months (95% CI: 13.2–20.6)

Clinical efficacy

A total of 68 patients were enrolled and received 537 cycles of chemotherapy with a median of 8 cycles (range: 1–30 cycles) per patient. Among the 68 enrolled patients, 66 patients were assessable for response. The reason for non-evaluability was premature discontinuation in two patients because of related adverse events after the first cycle. With a median follow-up time of 26 months, the median time to progression was 5.2 months (95% CI: 4.2–6.2, Fig. 1). The median overall survival was 16.9 months (95% CI: 13.2–20.6, Fig. 2). The overall response rate was 30.3% (20/66, 95% CI, 20–43%), including 1 complete (1.5%) and 19 partial (28.8%) responses. Response rate (33.3, 30 and 28.6%) did not vary significantly between numbers of prior chemotherapy regimens (0, 1 and 2 or more, respectively). Clinical benefit rate was 53.0% (35/66; 95% CI, 38–62%).

Table 2 Efficacy results of time to progression and overall survival by subset analysis

Subset	Evaluable no.	Median TTP (months)	*P* value	Median OS (months)	*P* value
	66	5.2		16.9	
Hormonal receptor			0.004		0.042
ER or PR positive	36	6.6		18.9	
ER and PR negative	30	3.4		13.8	
Her-2			>0.05		>0.05
Positive	10	5.7		17.5	
Negative	56	5.1		16.1	
Prior chemo			>0.05		>0.05
0	15	5.9		18.6	
1	30	4.9		16.0	
≥2	21	3.5		12.9	
Disease free interval			>0.05		0.048
>2 years	32	5.9		18.4	
≤2 years	30	4.9		10.6	
Liver metastases			>0.05		0.05
No	39	5.7		18.0	
Yes	27	4.9		11.0	
Metastatic sites			>0.05		>0.05
1	18	5.9		20.2	
2	20	4.9		12.3	
>2	28	5.1		14.0	

Table 2 shows the efficacy of TTP or OS by different subgroup analysis. Both TTP (6.6 months vs. 3.4 months, $P = 0.004$) and OS (18.9 months vs. 13.8 months, $P = 0.04$) were statistically longer in patients with ER/PR positive tumors compared to those with ER and PR double-negative tumors. There was a trend of a shorter median TTP and OS with more prior chemotherapy regimens, but it was not statistically significant. TTP was not associated with disease-free interval (≤2 years vs. >2 years) or with liver metastases (yes vs. no), but the OS showed the borderline significant differences ($P = 0.048$ and $P = 0.05$, respectively), likely reflecting the natural history of the disease.

Treatment-related toxicity

Toxicity profile is presented in Table 3. The most common (>20% patients) treatment-related adverse events were anorexia (73.5%), hand–foot syndrome (69.2%), nausea (66.2%), leukopenia (47.1%), diarrhea (30.9%), vomiting (29.4), neutropenia (25%), fatigue (23.5%). Most treatment-related adverse events were grade 1/2 in severity. The only grade 3/4 adverse event occurring in more than 5% of patients was grade 3 anorexia (7.5%). Grade 3 hand-foot syndrome was observed in only 3 patients (4.4%). There were no patients with febrile neutropenia or treatment-related deaths. The adverse events leading to dose reductions were hand–foot syndrome (2 patients) and diarrhea (1 patient). Eight cases of elderly patients over 65 years were able to complete the treatment process uneventfully.

Discussion

To our knowledge, this is a larger trial showing substantial efficacy and low toxicity of the all-oral combination of metronomic CTX plus capecitabine in patients with MBC pretreated with anthracycline and taxanes. We observed an ORR of 30.3%, a median TTP and OS of 5.2 months and 16.9 months, respectively.

MBC is considered incurable. The goal of therapy is therefore to reduce tumor burden and related symptoms and, ultimately, prolong survival, while maintaining quality of life by maximizing therapeutic potential and minimizing unnecessary toxicity. Optimal chemotherapy for MBC should be effective, well tolerated and convenient. Questionnaire-based studies have demonstrated that there was a striking 9:1 preference for oral chemotherapy rather than intravenous chemotherapy for patients, given the choice, provided efficacy was not sacrificed [34]. An all-oral combination of metronomic CTX plus capecitabine is more convenient and enables home-based therapy in patients with advanced cancer. Another advantage of this doublet is its much lower cost.

Table 3 Incidence of adverse events

	All		Grade 1		Grade 2		Grade 3		Grade 4	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%
Anorexia	50	73.5	37	54.4	8	11.8	5	7.5	0	0
Nausea	45	66.2	38	55.9	6	8.9	1	1.5	0	0
Vomiting	20	29.4	17	25.0	3	4.4	0	0	0	0
Diarrhea	21	30.9	17	25.0	3	4.4	1	1.5	0	0
Mucositis	12	17.6	10	14.7	1	1.5	1	1.5	0	0
Fatigue	16	23.5	15	22.1	1	1.5	0	0	0	0
Hyperbilirubinemia	6	8.9	5	7.4	1	1.5	0	0	0	0
AST/ALT elevation	6	8.9	4	5.9	1	1.5	1	1.5	0	0
Hand-foot syndrome	47	69.2	38	55.9	6	8.9	3	4.4	–	–
Arthralgia/Myalgia	8	11.8	7	10.3	1	1.5	0	0	0	0
Leukopenia	32	47.1	20	29.4	10	14.7	1	1.5	1	1.5
Neutropenia	17	25.0	11	16.2	3	4.4	2	2.9	1	1.5
Thrombocytopenia	8	11.8	4	5.9	3	4.4	1	1.5	0	0
Anemia	13	19.1	11	16.2	2	2.9	0	0	0	0

An analysis of our data showed that oral administration of the doublet achieved an ORR of 30.3%, which were consistent with reported results with single agent capecitabine in phase II trials [4–8], and comparable to the control arms of the phase III trials [9, 35–39]. All these phase III trials recruited heavily pretreated patients and the sample sizes were comparatively larger, making that the results coming from these trials are more reliable. Moreover, no significant difference is noted of ORR, TTP or OS for patients who failed first-line chemotherapy and those who failed two or more lines of chemotherapy. In MBC, it is common knowledge that the more chemotherapy regimens which patients received, the lower rates of objective responses achieved. Therefore, our results indicated that there is no cross-resistance between this regimen and other commonly used regimens. As expected, ER/PR positive patients had a better prognosis compared to ER and PR double-negative patients, in terms of both TTP and OS. But it is necessary to underline that the high heterogeneity of population enrolled in the study limits the efficacy results. For example, a small number of Her-2 positive patients who couldn't afford trastuzumab were enrolled in this study. Her-2 positive disease not receiving trastuzumab therapy usually has a worse outcome than Her-2 positive disease receiving trastuzumab in combination with chemotherapy. Tanaka et al. [40] reported that oral combination chemotherapy with capecitabine and cyclophosphamide in patients with metastatic breast cancer is effective with acceptable toxicities, with overall response rate of 35.6% and median progression-free survival was 199 days. Tong et al. [41] reported an "all-oral" regimen of capecitabine, idarubicin and cyclophosphamide for metastatic breast cancer was moderately active generally and well tolerated with median time to disease progression and median survival time were 13.4 and 23.7 months, respectively. Recently, Schott et al. confirmed our results at ASCO meeting 2010, reporting a SWOG phase II trial using the same doublet in a similar design, but using the fixed doses of cyclophosphamide (100 mg daily, days 1–14) and capecitabine (1,500 mg twice daily, days 8–21) [42].

This doublet has a good safety profile, with anorexia (7.5%), the only grade 3/4 adverse event occurring in more than 5% of patients. Grade 3 hand-foot syndrome was observed in only 3 patients (4.4%), and dose reductions were needed in only three patients. Our data were consistent with meta-analysis results suggesting that Esterns may tolerate 5-FU and its analogs better than Caucasians [43]. More importantly, rates of grade 3/4 adverse events occurring in more than 5% of patients were obviously lower than those of other capecitabine-containing doublets, used in the similar clinical settings in randomized phase III trials [9, 35–39]. Considering early clinical data, such as the classical CMF [44] and Canadian CEF [45] have extensively evaluated the safety of the combination of oral CTX and intravenous 5-FU, the metabolite of capecitabine, showing low and manageable toxicities, it is thus reasonable to infer that the doublet of capecitabine and CTX has a good safety profile.

Chemotherapy resistance remains a problem. Recently published papers suggested that it may be mediated by many factors, such as overexpression of drug efflux proteins, like MDR1 P-gp and altered β-tubulin isotype expression [1]. Overcoming resistance to these mechanisms represents a key therapeutic goal in the development of treatments for patients with MBC. In the present, our study provided a reasonable option for patients pretreated

with both anthrocycline and taxanes and who are not willing to undergo intravenous chemotherapy, have an indication to use capecitabine but have no access to or cannot afford molecular targeting agents.

Conclusion

Preclinical data show a synergy between capecitabine and CTX. Results from our study and other published data strongly recommend use of the all-oral doublet, metronomic CTX plus capecitabine, in patients with MBC, due to its efficacy, good tolerability, and ease of administration as well as lower cost.

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Conflict of interest The author(s) declare that they have no competing interests.

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