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ORIGINAL ARTICLE

Efficacy of synchronous stereotactic radiotherapy with temozolomide combined with whole brain radiotherapy in treating brain metastases originating from non-small cell lung cancer

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Summary

Purpose: *To investigate the efficacy and safety of synchronous stereotactic radiotherapy (SRT) with temozolomide (TMZ) combined with whole brain radiotherapy (WBRT) in treating brain metastases originating from non-small cell lung cancer (NSCLC).*

Methods: *The clinical data of 128 patients with brain metastases originating from NSCLC treated in the hospital from August 2015 to August 2017 were retrospectively analyzed. Among these patients, 64 received synchronous SRT with TMZ+WBRT (TMZ group), and 64 underwent SRT+WBRT (radiotherapy group). The clinical data of all patients were collected, and the short-term responses and adverse reactions after treatment were compared between the two groups. Additionally, the patients were followed up to record the overall survival (OS) and progression-free survival (PFS), and the factors probably affecting the prognosis of patients were analyzed.*

Results: *The incidence rate of nausea & vomiting was overtly higher in the TMZ group than that in the radiotherapy group (67.2% vs. 43.8%, p=0.008), while the incidence rate of other treatment-related adverse reactions showed no remarkable difference between the two groups (p>0.05). The follow-up results revealed that the median OS and PFS were (13.1±4.6) and (11.2±4.2) months in the TMZ group and (10.6±3.8) and (8.3±3.4) months in the radiotherapy group, respectively. According to log-rank test, the OS and PFS of patients in the TMZ group were evidently better than those in the radiotherapy group (p=0.041, p=0.025). Univariate and multivariate regression analyses suggested that the absence of extracranial metastasis, recursive partitioning analysis (RPA) class I, mini mental status examination (MMSE) score ≥27 points before radiotherapy, and treatment with TMZ were protective factors affecting the prognosis of patients.*

Conclusions: *Synchronous SRT with TMZ combined with WBRT is effective in treating patients with brain metastases originating from NSCLC, which can effectively improve the survival of patients and has tolerable adverse reactions. The absence of extracranial metastases, RPA class I, MMSE score ≥27 points before radiotherapy and treatment with TMZ are protective factors affecting the prognosis of patients.*

Key words: *temozolomide, stereotactic radiotherapy, whole brain radiotherapy, non-small cell lung cancer, brain metastases, efficacy*

Introduction

Non-small cell lung cancer (NSCLC) is a very frequent source of brain metastases in China, of which the incidence rate is 30-40% [1]. Brain metastases detected in patients indicate a very poor prognosis, and for their treatment, whole brain radiotherapy (WBRT) is the standard treatment meth-

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od, after which the median survival time is only 3-6 months [2,3]. To improve the efficacy in treating brain metastases, the application of chemotherapeutic and molecular targeted drugs has received much attention in recent years. However, the efficacy of many chemotherapy regimens is unfavorable since most chemotherapeutic drugs cannot penetrate the blood-brain barrier and bring about relatively severe neurotoxic side effects. Besides, standard targeted therapeutic drugs for epidermal growth factor receptor (EGFR)-mutant NSCLC, such as gefitinib and erlotinib, often lead to poor intracranial control due to their low blood-brain barrier penetration rates [4,5].

Temozolomide (TMZ), a new secondary imidazotetrazine-derived oral alkylating agent, can quickly penetrate the blood-brain barrier to lead to effective drug concentrations in the central nervous system. In addition, TMZ is convenient to take and well tolerated [6,7]. Moreover, many large clinical studies have proven the efficacy of TMZ, and TMZ has been recommended as a standard chemotherapeutic drug for malignant brain metastases by National Comprehensive Cancer Network (NCCN) guidelines since 2009 [8,9]. In this study, the clinical efficacy and safety of synchronous stereotactic radiotherapy (SRT) with TMZ+WBRT in brain metastases originating from NSCLC were explored, and the factors affecting the prognosis were analyzed.

Methods

General data

A total of 128 patients with brain metastases originating from NSCLC treated in our hospital from August 2015 to August 2017 were enrolled. Inclusion criteria: patients with extracranial lesions definitely diagnosed by histopathology and intracranial metastases definitely diagnosed via enhanced magnetic resonance imaging (MRI) examination, those with 1-5 brain metastasis/metastases less than 5 cm in diameter, those without dura/pia matereal metastases, those with Karnofsky score (KPS) ≥60 points, those with expected survival time greater than 3 months, those without a history of craniocerebral radiotherapy, those who never received TMZ, and those without significant abnormalities in blood routine and liver and kidney function examinations. Exclusion criteria: patients with brain metastases originating from pathological types other than NSCLC, those requiring surgery due to rather large intracranial metastases or pressing of important organs, those with uncontrolled existing extracranial metastases, or those previously undergoing radiotherapy or surgery for brain metastases. These patients were divided into synchronous stereotactic radiotherapy (SRT) with TMZ+WBRT (TME group, n=64) and SRT+WBRT (radiotherapy group,

Table 1. Baseline characteristics of the studied patients

Characteristics	*TMZ groupb (n=64) n (%)*	*Radiotherapy group (n=64) n (%)*	*p value*
Age (years)	58.0±10.3	56.6±9.7	0.430
Gender (Male/ Female)	39/25	34/30	0.475
Pathological type			0.527
Squamous cell carcinoma	16 (25.0)	12 (18.8)	
Adenocarcinoma	46 (71.9)	48 (75.0)	
Adenosquamous carcinoma	2 (3.1)	4 (6.2)	
Extracranial metastases			0.376
Yes	33 (51.6)	28 (43.8)	
No	31 (48.4)	36 (56.2)	
EGFR mutation			0.363
Yes	22 (34.4)	27 (42.2)	
No	42 (65.6)	37 (57.8)	
KPS score			0.559
70-90	44 (68.8)	47 (73.4)	
60-70	20 (31.2)	17 (26.6)	
RPA			0.474
Grade I	29 (45.3)	25 (39.1)	
Grade II	35 (54.7)	39 (60.9)	
MMSE score before treatment			0.579
<27	24 (37.5)	21 (32.8)	
≥27	40 (62.5)	43 (67.2)	

TMZ: Temozolomide; EGFR: Epidermal Growth Factor Receptor; KPS: Karnofsky performance status; RPA: recursive partitioning analysis; MMSE: Mini-mental State Examination.

n=64) based on different treatments. There were 73 males and 55 females with an average age of 57.8±10.1 years. There were no statistically significant differences in the baseline data before treatment between the two groups (Table 1) (p>0.05). This study was approved by the Ethics Committee of Yantai Yuhuangding Hospital Affiliated to Qingdao University. All patients enrolled were informed and signed the informed consent in accordance with Declaration of Helsinki.

Therapeutic regimens

WBRT: a linear accelerator (Elekta Synergy) was utilized for 6MV-X rays three-dimensional conformal whole brain irradiation. SRT: 6MV-X rays generated by the linear accelerator were used for irradiation from multi-angles and multi-dimensions with a multileaf collimator. A GE64-row spiral CT was adopted as the positioning device. The target volume was delineated. WBRT was carried out by three-dimensional conformal radiotherapy techniques, with a fraction dose of 2 Gy/time, a total dose of 36-40 Gy, and a treatment course of about 4 weeks. From 7-14 days after WBRT, SRT (complementary irradiation of lesions once every other day, three times a week) was performed, before which online verification was used to ensure that the errors in all directions were within 2 mm. Before SRT, additional positioning was not required, and the SRT planning for intracranial metastases from multi-angles and multi-dimensions using the multi-leaf collimator was developed, taking into account the number, volume and location of brain metastases and the physical strength score of patients. 80-90% isodose curves covered the planning target volume (PTV), the single dose was 6-8 Gy, 3 times a week, and the final intracranial lesion dose was 48-64 Gy. The dose to normal tissues including eyeballs, bilateral lens, bilateral optic nerves and optic chiasmas and medulla oblongata was within normal range.

During radiotherapy, TME capsules were given orally at the same time as follows: TME was taken from 3 day before radiotherapy at a dose of 75 mg/(m^2•d) once a day, 5 times a week, and 2 courses of TME chemotherapy (150-200 mg/m^2 once a day for 5 consecutive days, with 28 days as one course) were given after radiotherapy.

During radiotherapy and chemotherapy, patients were intravenously injected with mannitol and dexamethasone to reduce the symptom of cranial hypertension caused by cerebral edema, and metoclopramide or central antiemetics to relieve gastrointestinal symptoms caused by TME based on their clinical symptoms, and subcutaneously injected with granulocyte colony stimulating factor and recombinant human interleukin-11 in time for leukocyte and platelet therapy based on hematological changes. The blood routine and liver and kidney functions of patients were monitored during the treatment, and symptomatic treatment was promptly administered in case of abnormalities.

Observation indexes

At 2-3 months after radiotherapy, the patients were asked to receive enhanced MRI examination of the head in our hospital, so as to evaluate the efficacy according to the response evaluation criteria formulated by American Radiation Therapy Oncology Group (RTOG): complete remission (CR): complete disappearance of tumors shown on imaging examination and stable neurological function after discontinuation of hormones based on neurological examination for at least 4 weeks, without new lesions; partial remission (PR): over 50% of tumor regression shown on imaging examination and improved or stable neurological function in the case of administration of hormones at a steady dose based on neurological examination for at least 4 weeks, without new lesions; stable disease (SD): less than 50% of tumor regression shown on imaging examination and improved or stable neurological function based on neurological examination; and progressive disease (PD): over 25% increase in tumor size, presence of new lesions, or stable lesions but worsened neurological function based on neurological examination.

During treatment, the time and extent of adverse reactions were recorded, and acute radiation reactions, toxic effects of chemotherapy, and adverse reactions related to administration of TMZ were assessed in accordance with RTOG criteria, the Common Terminology Criteria Adverse Events (CTCAE) v3.0 and the National Cancer Institute Common Toxicity Criteria (NCI CTC) v4.0., respectively. Besides, the NCI CTC v4.0 was also employed to evaluate changes in neurological examination score before and after treatment and the effect of treatment on the nervous system function of patients, with -2 points for significant improvement, -1 point for slight improvement, 0 point for no change, +1 point for slight exacerbation, and +2 points for obvious exacerbation.

Overall survival (OS, the time from the date of the start of radiotherapy to the date of the death or the last follow-up of patients) and progression-free survival (PFS, the time from the date of the start of radiotherapy to the date of the progress of intracranial lesions or no progress but the death of patients) were used as patient survival indexes.

Statistics

SPSS 22.0 (IBM, Armonk, NY, USA) was utilized for statistical analysis. Measurement data were expressed as mean±standard deviation, and t-test was adopted for comparison between groups. Clinical data were compared via x^2 test or Fisher's exact test. Mann-Whitney U test was employed for short-term therapeutic effects and adverse reactions that were compared as unidirectional ordered rank data. The factors that might affect the prognosis of patients were subjected to univariate and multivariate analyses. The survival was analyzed via Kaplan-Meier curves and subjected to log-rank test. P<0.05 suggested that the difference was statistically significant.

Results

Comparisons of short-term responses

According to the efficacy evaluation performed on all patients at 2-3 months after treatment, there were 6 (9.3%) cases of CR, 46 (71.9%) cases of PR, 9 (14.1%) cases of SD and 3 (4.7%) cases of PD, with

an overall response rate of 81.3% (52/64) in the TMZ group, and 4 (6.2%) cases of CR, 40 (62.5%) cases of PR, 15 (23.4%) cases of SD and 5 (7.8%) cases of PD, with an overall response rate of 68.8% (44/64) in the chemotherapy group. The overall response rate had no statistically significant difference between the two groups (p=0.103) (Table 2).

Before treatment, 47 cases and 52 cases with neurological symptoms (headache, nausea, vomiting, memory loss and cognitive impairment) were observed in the TMZ group and chemotherapy group, respectively. Based on neurological function evaluation after treatment via NCI CTC v4.0, there were 25 and 21 cases of significant improvement and 13 and 16 cases of slight improvement in the two groups, respectively, and the remission rate of neurological symptoms was 80.9% and 71.2% in the two groups, respectively. The differences were not statistically significant between two groups (p=0.349).

Comparisons of adverse reactions

Adverse reactions of patients detected during treatment were mainly hematological toxic-

Table 2. Clinical effective rates of the two studied groups

	TMZ group (n=64) *n (%)*	*Radiotherapy group (n=64)* *n (%)*	*p value*
CR	6 (9.3)	4 (6.2)	
PR	46 (71.9)	40 (62.5)	
SD	9 (14.1)	15 (23.4)	
PD	3 (4.7)	5 (7.8)	
ORR	52 (81.3)	44 (68.8)	0.103

TMZ: Temozolomide; CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; ORR: Objective response rate.

Table 3. Comparison of adverse reactions and complications of patients in the two studied groups

Parameters	*TMZ group (n=64)*		*Radiotherapy group (n=64)*		*p value*
	Grade I-II *n (%)*	*Grade III-IV* *n (%)*	*Grade I-II* *n (%)*	*Grade III-IV* *n (%)*	
Nausea / Vomiting	38 (59.4)	5 (7.8)	28 (43.8)	0 (0)	0.008
Diarrhea	27 (42.2)	0 (0)	22 (34.4)	0 (0)	0.363
Headache	39 (60.9)	0 (0)	35 (54.7)	0 (0)	0.474
Leukopenia	33 (51.6)	6 (9.4)	30 (46.9)	4 (6.3)	0.372
Thrombocytopenia	31 (48.4)	8 (12.5)	32 (50.0)	5 (7.8)	0.719

TMZ: Temozolomide.

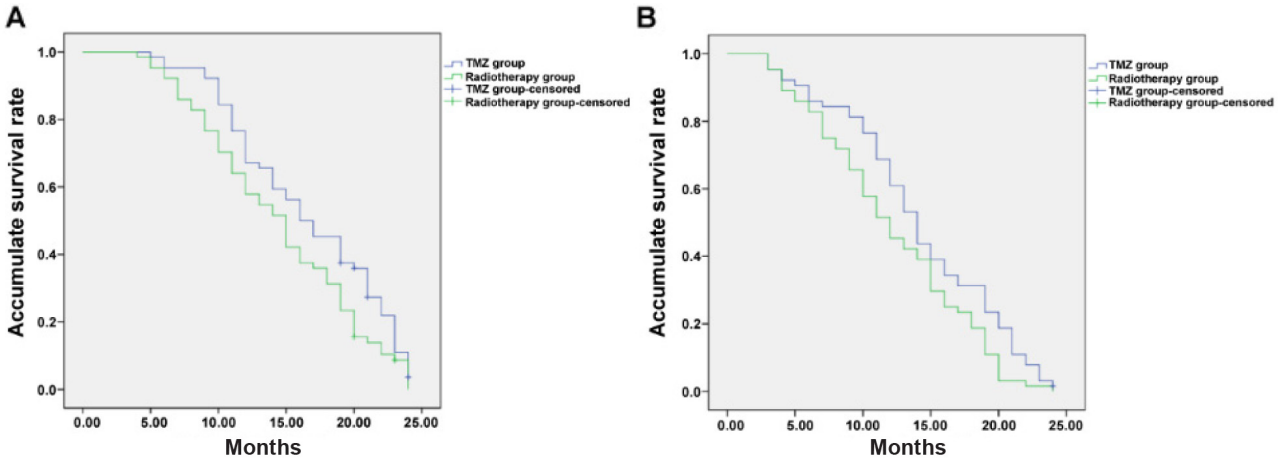

Figure 1. Kaplan-Meier survival curves of patients in the TMZ group and radiotherapy group. **A:** The overall survival rate of patients in the TMZ group was significantly higher than that of radiotherapy group (p=0.041). **B:** The progression-free survival rate of patients in the TMZ group was significantly higher than that of radiotherapy group (p=0.025).

ity (grade I-II leukopenia and thrombocytopenia) and gastrointestinal toxicity (nausea & vomiting, and diarrhea). Hepatotoxicity, nephrotoxicity or cardiotoxicity and treatment discontinuation or drug dose reduction due to adverse reactions were not found during treatment. The incidence rate of nausea & vomiting was overtly higher in the TMZ group than in the radiotherapy group (67.2% *vs.* 43.8%, p=0.008), while there was no statistically significant difference in the incidence of other treatment-related adverse reactions between the two groups (p>0.05). (Table 3).

Follow-up results of the survival time of patients

All the 128 patients were followed up for 4-24 months until July 2019. The mean OS and PFS were 13.1±4.6 and 11.2±4.2 months in the TMZ group and 10.6±3.8 and 8.3±3.4 months in the radiotherapy group, respectively. Survival curves were plotted by Kaplain-Meier method (Figure 1) and log-rank test revealed that the OS and PFS of patients were clearly superior in the TMZ group to those in the radiotherapy group, displaying statistically significant differences (p=0.041, p=0.025).

Analysis of factors affecting the prognosis of patients

The survival data obtained in this study were hierarchically analyzed based on various factors that might be related to the prognosis. Age, pathological type, number of brain metastases, presence or absence of extracranial metastasis, KPS score before treatment, recursive partitioning analysis (RPA) class, mini mental status examination (MMSE) score before treatment, and treatment with or without TMZ were included in the univariate analysis, and the results suggested that the number of brain metastases, presence or absence of extracranial metastasis, RPA class, MMSE score before treatment, and treatment with or without TMZ affected the median OS and PFS of patients (Table 4). The results of Cox multivariate regression analysis demonstrated that the presence or absence of extracranial metastasis, RPA class, MMSE score before treatment, and treatment with

Table 4. Univariate analysis of predictors for mOS (months) and mPFS (months) in non-small cell lung cancer patients with brain metastases

Parameters	*Cases*	*OS (months)*	*p value*	*PFS (months)*	*p value*
Age (years)			0.492		0.264
≤50	74	12.4±3.9		11.0±4.4	
>50	54	11.9±4.3		9.7±3.4	
Pathological type			0.152		0.138
Squamous cell carcinoma	28	12.9±3.6		11.5±5.2	
Adenocarcinoma	94	10.8±3.4		9.6±3.1	
Adenosquamous carcinoma	6	9.9±3.1		8.7±3.7	
Number of metastases			0.001		0.001
<3	88	16.6±5.4		13.3±4.5	
≥3	40	9.4±4.0		8.2±3.2	
Extracranial metastases			0.001		0.001
Yes	61	10.3±4.2		8.8±4.1	
No	67	15.6±3.6		13.8±5.4	
KPS score			0.129		0.104
70-90	91	13.8±3.8		11.2±4.3	
60-70	37	11.8±4.9		9.6±3.6	
RPA			0.001		0.001
Grade I	54	18.3±4.4		15.5±5.0	
Grade II	74	10.4±4.1		8.5±4.2	
MMSE score before treatment			0.001		0.001
<27	45	10.7±3.3		9.0±4.0	
≥27	83	15.9±3.1		13.1±4.7	
Treatment			0.001		0.001
TMZ+Radiotherapy	64	13.1±4.6		11.2±4.2	
Radiotherapy	64	10.6±3.8		8.3±3.4	

OS: Overall survival; PFS: Progression-free survival; KPS: Karnofsky performance status; RPA: recursive partitioning analysis; MMSE: Mini-mental State Examination.

Table 5. Multivariate Cox regression analysis of predictors for non-small cell lung cancer patients with brain metastases

Parameters	*OS*			*PFS*		
	HR value	*95% CI*	*p value*	*HR value*	*95% CI*	*p value*
Number of metastases	0.819	0.654-1.356	0.109	0.763	0.582-1.147	0.240
Extracranial metastases	0.077	0.041-0.258	0.021	0.297	0.181-1.060	0.039
RPA	0.387	0.065-0.613	0.006	0.292	0.103-0.484	0.007
MMSE score before treatment	0.179	0.046-0.342	0.003	0.081	0.042-0.394	0.001
TMZ+Radiotherapy	0.190	0.115-0.451	0.001	0.104	0.093-0.446	0.002

OS: Overall survival; PFS: Progression-free survival; RPA: Recursive partitioning analysis; MMSE: Mini-mental State Examination; HR: Hazard Ratio; CI: Confidence interval.

or without TMZ were correlated with the prognosis of patients. The absence of extracranial metastasis, RPA class I, MMSE score ≥27 points before radiotherapy, and treatment with TMZ were protective factors affecting the prognosis of patients (Table 5).

Discussion

As one of the most serious complications in patients with NSCLC, brain metastases have extremely poor prognosis, with a median survival time of 4-6 weeks in untreated patients and a mean survival time of 3-6 months in patients undergoing comprehensive treatment. Currently, supportive treatment, surgical treatment, radiotherapy, intrathecal chemotherapy, systemic chemotherapy and molecular targeted therapy are mainly adopted for the treatment [10], but there is no standard treatment strategy [11].

WBRT, a cornerstone for the treatment of brain metastases, has been applied for decades and proved, in several clinical trials on WBRT conducted by RTOG in the 1990s, to be able to improve the survival time of patients with brain metastases by 2-4 months [12,13]. However, the radiation dose of lesions cannot achieve radical therapy, and about 50% of patients with brain metastases may have new lesions in the brain after received WBRT alone since WBRT is limited by the tolerance dose for normal brain tissues. Excessive dose of normal brain tissues after WBRT may cause neurocognitive dysfunctions in patients with brain metastases. With the development Medicine, SRT has emerged in recent years, which can better protect the normal brain tissues around the lesion and important structures like the brain stem, visual pathways and cerebrospinal fluid circulation pathways. The results of a phase III randomized controlled clinical study (RTOG9508) with a sample size of 331 patients published by American RTOG in 2004 have confirmed the therapeutic value of WBRT + SRT in brain metastases [14].

As a recently new alkylating agent taken orally to treat primary malignant gliomas in the brain, TMZ has such outstanding features as small molecule, fat solubility and high bioavailability, which is converted into anti-tumor activity substances after entering the central nervous system. Besides, its toxic and side effects are less, and its blood-brain barrier permeability is high (about 30-40% of plasma concentration) based on observations in clinical practice. As a result, TMZ is gradually applied in the treatment of brain metastases, and achieves a good therapeutic effect. A synergistic effect shall be obtained when co-application with radiotherapy [8,9]. Moreover, several large clinical studies have confirmed the efficacy of TMZ that has been recommended as a standard therapeutic drug for malignant brain metastases by NCCN guidelines since 2009 [15,16]. Numerous studies have demonstrated that combined treatment of TMZ+WBRT improves the local control rate, prolongs the PFS, and clearly improves the quality of life of patients with brain metastases [7,17]. A phase III randomized controlled clinical trial in patients with brain metastases (1-3 lesions) originating from NSCLC conducted by Sperduto et al showed that no significant difference was detected in the survival rate among WBRT alone group, WBRT+SRT group and WBRT+SRT+TMZ/erlotinib group [4]. Another meta-analysis including 1028 patients and 18 studies by Bai et al [18] pointed that combination with TMZ can slightly prolong the survival time.

In this study, it was uncovered that the overall response rate and the remission rate of neurological symptoms were 81.3% and 80.9% in the TMZ group and 68.8% and 71.2% in the radiotherapy group, respectively, and the differences were of no statistical significance (p=0.103, p=0.349), similar to those in previous reports. The mean OS and PFS were 13.1±4.6 and 11.2±4.2 months in the TMZ group and 10.6±3.8 and 8.3±3.4 months in the radiotherapy group, respectively, superior to those in previous reports. This may be because in

this study, the patients enrolled were at RPA class 1-2, and the administration of certain molecular targeted drugs and chemotherapeutic drugs for systemic maintenance was not prohibited, leading to better control of extracranial lesions in these patients and thus prolonging the OS. Besides, TMZ was well tolerated by patients, and all adverse reactions were alleviated after symptomatic treatment. It was discovered in this study that the absence of extracranial metastasis, RPA class I, MMSE score ≥27 points before radiotherapy, and treatment with TMZ were protective factors affecting the prognosis of patients, basically in line with the findings of previous studies [19,20].

This study is a single-center retrospective study and has certain limitations. The sample size was small, and the follow-up time was short. Hence, prospective multicenter randomized controlled studies with a large sample size and a more rigorous and scientific design are needed in the future to verify the results in this study, providing a reference for the selection of therapeutic schedules for such patients.

Conclusions

Synchronous SRT with TMZ combined with WBRT is an effective method in treating patients with brain metastases originating from NSCLC, which is capable of effectually improving the survival of patients, with tolerable adverse reactions. The absence of extracranial metastases, RPA class I, MMSE score ≥27 points before radiotherapy and treatment with TMZ are protective factors positively affecting the prognosis of patients.

Conflict of interests

The authors declare no conflict of interests.

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