

Comparative efficacy of whole-brain radiotherapy with and without elemene liposomes in patients with multiple brain metastases from non-small-cell lung carcinoma

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ABSTRACT

Purpose We explored and compared the clinical effects of whole-brain radiotherapy (WBRT) with and without elemene liposomes in patients with multiple brain metastases from non-small-cell lung carcinoma (NSCLC).

Methods We retrospectively analyzed 62 patients with multiple brain metastases from NSCLC who received WBRT (30 Gy in 10 fractions) at Shengjing Hospital of China Medical University from January 2012 to May 2013. In 30 patients, elemene liposomes (400 mg) were injected intravenously via a peripherally inserted central catheter for 21 consecutive days from the first day of radiotherapy. Overall survival (OS) and nervous system progression-free survival (NPFs) for the two groups were compared by Kaplan–Meier analysis. Factors influencing NPFs were examined by Cox regression analysis. Chi-square or Fisher exact tests were used for group comparisons.

Results The median OS was 9.0 months in the WBRT plus elemene group and 7.8 months in the WBRT-alone group ($p = 0.581$); the equivalent median NPFs durations were 5.2 months and 3.7 months ($p = 0.005$). Patient treatment plan was an independent factor associated with NPFs ($p = 0.002$). Tumour response and disease-control rates in the WBRT plus elemene group were 26.67% and 76.67% respectively; they were 18.75% and 62.5% in the WBRT group ($p = 0.452$). Compared with the patients in the WBRT-alone group, significantly fewer patients in the WBRT plus elemene group developed headaches ($p = 0.04$); quality of life was also significantly higher in the WBRT plus elemene group both at 1 month and at 2 months ($p = 0.021$ and $p = 0.001$ respectively).

Conclusions The addition of elemene liposomes to WBRT might prolong NPFs in patients with multiple brain metastases from NSCLC, while also reducing the incidence of headache and improving patient quality of life.

Key Words Elemene liposomes, multiple brain metastases, non-small-cell lung carcinoma, whole-brain radiotherapy

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INTRODUCTION

About 20%–40% of patients with non-small cell lung cancer (NSCLC) develop brain metastasis, with a consequently poor prognosis¹. Whole-brain radiotherapy (WBRT), either alone or combined with surgery, and stereotactic radiosurgery have been the standard treatments for brain metastasis, although overall survival (OS) after WBRT is only 4–5 months. The presence of the blood–brain barrier makes it difficult for chemotherapeutic drugs to reach

intracranial lesions², and radiosensitizing agents thus represent a means of improving survival and quality of life for patients with brain metastases, while reducing the side effects of chemotherapy.

Elemene (1-methyl-1-vinyl-2,4-diisopropenyl-cyclohexane) is a natural compound found in a variety of plants. It occurs as β , γ , and δ isomers, with β -elemene accounting for 85% of the total³. In numerous experiments, elemene has demonstrated inhibitory effects on leukemia and on breast, prostate, lung, and metastatic brain

cancers⁴, but its effect on brain metastases from NSCLC when combined with radiotherapy remains unclear. In the present study, we aimed to compare nervous system progression-free survival (nPFs), OS, quality of life, adverse reactions after radiotherapy, tumour control rate, and response rate in patients with intracranial metastatic lesions of NSCLC treated with either WBRT alone or WBRT in combination with elemene.

METHODS

Patients

The study enrolled 62 patients with multiple brain metastases from NSCLC treated at Shengjing Hospital of China Medical University from January 2012 to May 2013. The last follow-up occurred in May 2015. All patients were diagnosed with NSCLC by pathology, and multiple brain metastases were diagnosed by magnetic resonance imaging or enhanced computed tomography. Inclusion criteria were no need for immediate chemotherapy, measurable lesions, no history of radiotherapy, no chemotherapy during the preceding 28 days, a Glasgow coma score of 14 or greater, a Karnofsky score of 70 or greater, 3 or fewer extracranial metastatic lesions, and Radiation Therapy Oncology Group recursive partitioning analysis type I or II⁵. Pregnant women and children were excluded, as were patients with other current or prior malignant intracranial tumours or with a single brain metastasis suitable for stereotactic radiosurgery or surgical resection, and patients with severe damage to liver and kidney function.

Study Design and Treatment

All patients received WBRT once daily, for 10 days, to a total dose of 30 Gy delivered using a 6 MV X-ray linear accelerator. The overall treatment duration was 2 weeks. Patients were placed in the supine position with customized immobilization masks. Mannitol and glucocorticoids were administered to reduce intracranial pressure, according to the patient's symptoms. Elemene liposomes 400 mg [98% pure β -elemene (Dalian Holley Kingkong Pharmaceutical, Dalian, P.R.C.)] added to 500 mL 5% glucose saline were delivered through a peripherally inserted central catheter for 21 consecutive days from day 1 of radiotherapy. The elemene liposomes were obtained from the Traditional Chinese Medicine *Curcuma wenyujin*, a herb that grows in Zhejiang, P.R.C. In the study group, 32 patients received WBRT alone, and 30 received WBRT plus elemene.

Assessments

Baseline assessments included medical history, physical examination, nervous system examination, routine laboratory tests, chest and abdominal computed tomography, and cranial computed tomography or magnetic resonance imaging. Cranial magnetic resonance imaging was performed 4 and 8 weeks after WBRT to evaluate toxic reactions and clinical efficacy, and then every 2 months until disease progression or death.

We defined nPFs as clinical or radiographic progression (or both), including a Mini Mental State Examination score 3 points lower than baseline; movement intensity, vision, and gait decreased by 3 points, or vision and gait decreased

2 points; Karnofsky score decreased by 10 points or more (all evaluated in the 6th week or thereafter); increase in dexamethasone dosage from the 6th week onward; sum of maximum diameters of the metastases with a baseline size of 0.5 cm or more increased by 20% or more (with the minimum sum of the maximum diameters at the start of the study as reference); and appearance of new disease foci.

Tumour response was classified as follows:

- Complete remission: No clinical manifestation and imaging suggested no tumour residue.
- Partial response: Clinical exam or imaging showed a decrease in longest tumour diameter of 30% or more.
- Progressive disease: Sum of longest diameters increased by 20% or more.

Tumours not meeting the foregoing criteria were classified as showing no change. The tumour response rate was defined as the proportion of all patients experiencing either complete remission or partial response, and the tumour control rate was defined as the proportion of all patients experiencing complete remission, partial response, or no change. Performance status was evaluated by Karnofsky score, with a score of 100 indicating perfect health and 0 indicating death.

Toxicity was scored using the U.S. National Cancer Institute's *Common Terminology Criteria for Adverse Events*, version 3.0. Only grade 3 or 4 toxic reactions were recorded. Quality of life was assessed using the EuroQol EQ-5D-3L (EuroQol Group, Rotterdam, Netherlands) questionnaire.

Statistical Methods

The OS and nPFs were compared using the Kaplan–Meier method. Chi-square or Fisher exact tests were used for group comparisons, and Cox regression analysis was used to examine the factors influencing nPFs. All data were analyzed using the IBM SPSS Statistics software application (version 22.0; IBM, Armonk, NY, U.S.A.), and $p < 0.05$ was considered to indicate statistical significance.

RESULTS

Baseline Characteristics

Table 1 shows general patient information. All clinical features in the two groups were comparable ($p > 0.05$).

OS

Median follow-up was 8.9 months (range: 1.8–24 months). The 1-year survival rates were 21.9% in the WBRT group and 30.0% in the WBRT plus elemene group. Median OS duration was 7.8 months [95% confidence interval (CI): 5.31 to 10.30 months] in the WBRT group and 9.0 months [95%CI: 6.99 to 11.01 months; $p = 0.581$; Figure 1(A)] in the WBRT plus elemene group.

nPFs

The proportion of nPFs occurring at the 5th month in patients in the WBRT group was 21.9%; in the WBRT plus elemene group, it was 53.5%. The median time to nPFs in the WBRT group was 3.7 months (95%CI: 3.28 to 4.12 months); in the WBRT plus elemene group, it was 5.2 months [95%CI:

TABLE I Baseline patient characteristics

Variable	Patient group		<i>p</i> Value
	WBRT	WBRT plus elemene	
Patients (<i>n</i>)	32	30	
Age (years)			
Median	62	61.5	
Range	37–76	32–75	
Sex [<i>n</i> (%)]			0.88
Men	24 (77.14)	22 (74.07)	
Women	8 (22.86)	8 (25.93)	
RTOG RPA [<i>n</i> (%)]			0.28
I	9 (28.57)	5 (29.63)	
II	23 (71.43)	25 (70.37)	
Metastatic foci [<i>n</i> (%)]			0.82
≤5	14 (43.75)	14 (46.67)	
>5	18 (56.25)	16 (53.33)	
Longest diameter (cm)			
Median	2.1	2.3	0.477
Range	0.8–5.2	0.5–4.9	
Karnofsky PS [<i>n</i> (%)]			0.479
70	8 (25)	12 (40)	
80	18 (56.25)	13 (43.33)	
90	5 (15.63)	5 (16.67)	
100	1 (3.12)	0	
Pathologic type [<i>n</i> (%)]			0.896
Adenocarcinoma	18 (56.25)	16 (53.33)	
Squamous cell carcinoma	14 (43.75)	13 (43.33)	
Large-cell carcinoma	0	1 (3.34)	

RTOG = Radiation Therapy Oncology Group; RPA = recursive partitioning analysis; PS = performance status.

3.59 to 6.81 months; $p = 0.005$; Figure 1(B)]. By Cox regression analysis, treatment with or without elemene was a significant factor influencing nPFS (Table II).

Tumour Control Rate and Response Rate

At 8 weeks after treatment, the tumour response and control rates were both higher in the WBRT plus elemene group than in the WBRT-alone group, although the differences were nonsignificant (Table III).

Toxic Reactions

Grade 3 or 4 toxic reactions occurred in 65.62% of the patients in the WBRT group and in 50.00% of the patients in the WBRT plus elemene group. Significantly fewer patients in the latter group developed headaches ($p = 0.04$), but no significant differences between the groups in any other adverse reactions was observed ($p > 0.05$, Table IV).

Quality of Life

At both 1 and 2 months after treatment, patient quality of life (adjusted for baseline interference) was significantly higher in the WBRT plus elemene group than in the WBRT-alone group ($p = 0.021$ and $p = 0.001$ respectively, Table V).

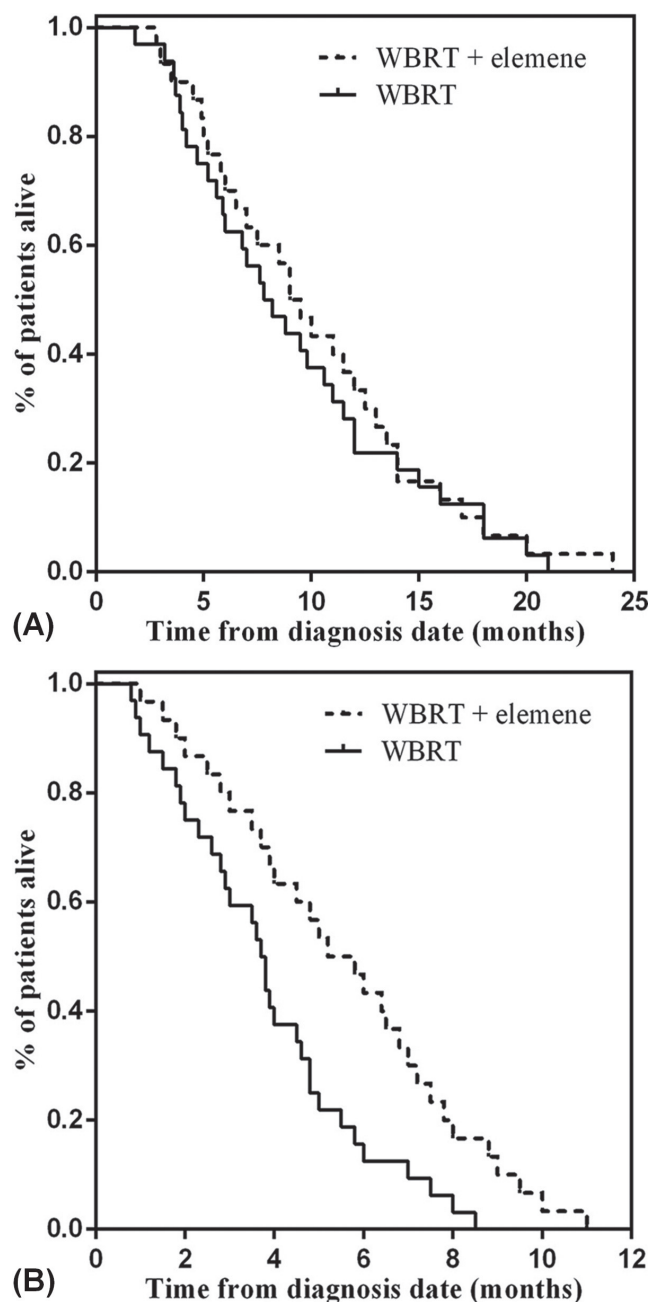


FIGURE 1 Survival curves for patients treated with whole-brain radiotherapy (WBRT) or with WBRT and elemene. (A) Overall survival: No significant difference between the patient groups was observed ($p > 0.05$). (B) Nervous system progression-free survival (nPFS): Patients who received elemene experienced better nPFS than did those receiving radiotherapy alone ($p < 0.05$).

DISCUSSION

Most patients with brain metastases from NSCLC have multiple brain metastases or extensive extracranial metastases, and short-term palliative WBRT has been regarded as the standard treatment in such cases. Given the poor prognostic factors in these patients (for example, performance status, age, and severity of extracranial disease), almost

half die from progression of their intracranial disease⁶. Resistance to radiotherapy and treatment interruptions in patients with adverse reactions after radiotherapy contribute to the poor prognosis in lung cancer with brain metastasis.

Elemene is a compound that can be extracted from various plants, with β -elemene being the active ingredient. The antitumour activity of elemene was first discovered by Chinese researchers in the 1980s, and since then elemene has become a widely used antitumour drug. Many preclinical studies and clinical trials of elemene have demonstrated broad-spectrum antitumour activity, good patient tolerance, and an ability to penetrate the blood–brain barrier, among other advantages^{7,8}. However, β -elemene has poor water solubility, poor stability, and low bioavailability, leading to relatively low bioavailability after oral administration⁹. However, elemene liposomes demonstrate improved permeability and retention. Liposomes allow drugs to be absorbed more quickly and completely,

and liposome encapsulation can improve drug stability, lymphatic directivity, long-term sustained release, and passive or physiologic targeting to tumour tissues, as well as reduced toxicity^{10,11}.

Compared with other anticancer drugs, elemene has a low molecular weight and a lipophilic nature, enabling it to penetrate the blood–brain barrier¹², as demonstrated by the detection of elemene molecules in brain tissues after intragastric and intravenous administration in a mouse model using G422 glioma cells³. Elemene was shown to improve quality of life and prolong survival duration in a study of 9 neuroglioma patients and 11 patients with metastatic brain tumours¹³. Other studies have verified the therapeutic efficacy of elemene for malignant brain tumours¹⁴, suggesting that β -elemene can effectively inhibit the growth and proliferation of brain tumour cells. The antitumour effect of elemene appears to be related to the induction of apoptosis via the apoptotic signalling pathway. The elemene analogues Lr-1 and Lr-2 appear to have similar anti-brain tumour effects¹⁴.

In the present study, nRRS was higher in patients who received elemene than in those receiving radiotherapy alone, thus confirming elemene's antitumour efficacy and its ability to penetrate the blood–brain barrier. The brain tumour response and control rates were higher in metastatic patients treated with WBRT plus elemene than in those treated with WBRT alone, although the differences were nonsignificant, possibly because of the small sample size.

Several studies have shown a radiosensitizing effect of elemene. Jiang *et al.*¹⁵ showed that, in addition to promoting tumour cell apoptosis directly, β -elemene also exerts a radiosensitizing effect on lung adenocarcinoma A549 cells through upregulation of p53 expression and inhibition of Bcl-2 expression. Another study by Zou *et al.*¹⁶ demonstrated that the molecular mechanisms responsible for the radiosensitizing effect might involve the downregulation of DNA-dependent protein kinase catalytic subunit gene expression. Li *et al.*¹⁷ established a lung tumour model in female athymic BALB/cnu/nu mice, and showed that β -elemene (45 mg/kg) had the potential to reduce radiation-induced expression of survivin and hypoxia inducible factor 1 α proteins, which were probably the targets of β -elemene. The results of the present study found no significant difference in os between patients treated with and without elemene, again possibly because of the small sample size. Furthermore, progression of extracranial disease can also influence os.

Four studies¹⁸ examining 445 cases of NSCLC showed that the physical state score was higher in patients treated with chemotherapy combined with elemene than in those

TABLE II Factors influencing nervous system progression-free survival, by Cox regression analysis

Variable	HR	95% CI	p Value
Elemene treatment			
WBRT	Reference		
WBRT plus elemene	2.575	1.418 to 4.677	0.002
Sex			
Men	Reference		
Women	0.902	0.460 to 1.770	0.765
Age (years)	1.005	0.977 to 1.033	0.744
RTOG RPA			
I	Reference		
II	1.628	0.779 to 3.405	0.195
Brain metastases			
≤5	Reference		
>5	0.693	0.381 to 1.263	0.231
Largest brain metastasis (cm)	0.940	0.732 to 1.207	0.627
KPS			
70	Reference		
80	0.507	0.057 to 4.484	0.541
90	0.753	0.084 to 6.748	0.8
Tumour histologic type			
Adenocarcinoma	Reference		
Squamous cell carcinoma	0.282	0.03 to 2.615	0.265

HR = hazard ratio; CI = confidence interval; RTOG = Radiation Therapy Oncology Group; RPA = recursive partitioning analysis.

TABLE III Tumour response and tumour control rates in patients treated with whole-brain radiotherapy (WBRT) or WBRT and elemene at 8 weeks after treatment

Study group	Pts (n)	Response (n)				Tumour response rate (%)	Tumour control rate (%)	Chi-square	p Value
		Complete	Partial	Progressive disease	No change				
WBRT	32	0	6	12	14	18.75	62.5	1.588	0.452
WBRT and elemene	30	0	8	7	15	26.67	76.67		

TABLE IV Grades 3 and 4 toxic reactions in patients treated with whole-brain radiotherapy (WBRT) or WBRT and elemene

Reaction	Study group [n (%)]		p Value
	WBRT (n=32)	WBRT and elemene (n=30)	
Any reaction	21 (65.63)	15 (50)	0.21
Fatigue	16 (50)	11 (36.67)	0.29
Weight loss	6 (18.75)	3 (10)	0.33
Nausea	3 (9.38)	1 (3.33)	0.33
Dry eye	4 (12.5)	2 (6.67)	0.44
Pain (neural headache)	20 (62.5)	11 (36.67)	0.04

TABLE V Quality of life in patients treated with whole-brain radiotherapy (WBRT) or WBRT and elemene

EuroQol EQ-5D follow-up	WBRT (n=32)		WBRT and elemene (n=29 ^a)		F statistic	p Value
	Median	IQR	Median	IQR		
Baseline	0.69	0.61, 0.74	0.71	0.63, 0.75		
Month 1	0.54	0.48, 0.68	0.65	0.62, 0.73	5.655	0.021
Month 2	0.49	0.41, 0.62	0.66	0.54, 0.72	12.926	0.001

^a One patient died before the 2-month follow-up.

treated with chemotherapy alone (54.05% vs. 29.60%), and the adverse effects reported by fifteen studies¹⁸ included phlebitis, fever, nausea, vomiting, allergy, leucopenia, alopecia, and liver function damage. Phlebitis and allergy were more common in patients treated with chemotherapy combined with elemene; leucopenia was less common¹⁸. The most common adverse effects associated with elemene are mild fever, gastrointestinal reactions, and local pain, but not bone marrow suppression or liver and kidney toxicities¹⁹. The results of the present study confirmed that elemene could improve patient quality of life and reduce the incidence of grade 3 or 4 headache, which could be related to its function in controlling intracranial metastases and reducing intracranial edema. Previous reviews have also reported that plant-derived drugs can reduce radiation damage by cleaning up and producing active oxygen and inducing apoptosis²⁰.

As a potential anticancer drug, β -elemene has broad application prospects associated with 3 key advantages: it can be sourced from more than 50 different herbs and plants; its potent anticancer effects include inhibiting angiogenesis, inducing tumour-cell apoptosis, enhancing radiation sensitivity, and improving chemotherapeutic effects in combination with other anticancer drugs. Furthermore, it exerts only slight side effects, with mild liver and kidney function damage and no bone marrow suppression²¹.

CONCLUSIONS

Elemene liposomes combined with WBRT might prolong nPFS, reduce the incidence of headache, and improve quality of life for patients with brain metastases from NSCLC. Its

relatively low cost, low toxicity, and ability to penetrate the blood–brain barrier mean that elemene liposomes potentially have wide clinical prospects. However, the present work is only a single-centre, small, hypothesis-generating retrospective study. To explore whether elemene influences or improves the quality of life in patients with brain metastases, further large-scale prospective multicentre randomized controlled trials are needed.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

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