Evidence of elemene injection combined radiotherapy in lung cancer treatment among patients with brain metastases

A systematic review and meta-analysis

Xutao Jiang, MD, Tesfaldet Habtemariam Hidru, MD, Zhuo Zhang, PhD, Yu Bai, MD, Lingchao Kong, MD, Xiaofeng Li, PhD

Abstract

Background: This review evaluates the effectiveness and safety of elemene injection combined radiotherapy in the treatment of lung cancer with brain metastases.

Methods: A systematic literature research was conducted from EMBASE, Cochrane Library, PubMed, Chinese biomedical database, Chinese scientific journal database, China knowledge resource integrated database, and WanFang Database from established to July 2016 without language restriction. The Cochrane Collaboration tool was used to evaluate the risk of bias. All statistical analyses were conducted with STATA (version 14.0) and RevMan (version 5.3).

Results: Eleven randomized controlled trials (765 patients) were included for determining the effectiveness and safety of elemene combined with radiotherapy in the treatment of lung cancer with brain metastases. Objective response rate (ORR) (odds ratio (OR) = 2.89, 95% confidence interval (95% CI) 2.04–4.08, P < .00001) and symptoms (OR = 4.06, 95% CI 2.00–8.25, P = .001) improved more in the elemene-based combination treatment group than in the radiotherapy-alone control group. The Karnofsky Performance Status (KPS) score was used to measure patients’ improvement rate. The patients who were treated with elemene-based combination with radiotherapy were higher than those patients who were treated with radiotherapy alone (OR = 3.51, 95% CI 2.20–5.61, P < .00001). The incidence of bone marrow suppression (OR = 0.27, 95% CI 0.11–0.68, P = .006) and leukopenia (OR = 0.23, 95% CI 0.12–0.46, P < .00001) decreased in the elemene-based combination treatment group by radiotherapy significantly.

Conclusions: The elemene injection combined radiotherapy in the treatment of lung cancer with brain metastases appears to improve the treatment response rate and alleviated symptoms. The combined treatment has shown positive impact to reduce adverse reactions and improve quality of life.

Abbreviations: CBM = Chinese biomedical database, CI = confidence intervals, CNKI = China knowledge resource integrated database, CONSORT = consolidated standards of reporting trials, KPS = Karnofsky performance status, OR = odd ratios, ORR = objective response rate, PRISMA = preferred reporting items for systematic reviews and meta-analyses, RCTs = randomized controlled trials, VIP = Chinese scientific journal database, WBRT = whole-brain radiation therapy.

Keywords: brain metastases, elemene injection, lung cancer, meta-analysis, radiotherapy

1. Introduction

Lung cancer, one of the most common cancers with a nature of malignancy, imposes a serious damage to human health in the world. In 2012, it was estimated that there were 1.8 million (13% of total) new cases of lung cancer globally. It was the leading cause of death among malignant tumor in China, which accounts for more than 369,000 deaths in both rural and urban areas of the country. The incidence of lung cancer continued to increase worldwide. Risk factors may include high rates of smoking, aging, and environmental changes that caused by industrialization and urbanization.

Brain metastasis, a lethal complication of lung cancer, is the main reason for the failure of treatment and poor prognosis. Surgical treatment, radiotherapy, chemotherapy, and molecular targets agents comprise the treatment protocol for lung cancer patients with brain metastases. The whole-brain radiation therapy (WBRT) is the most widely used therapeutic modality among these treatments; however, it induces severe adverse reactions, including neuroendocrine dysfunction and progressive dementia, which limit the efficacy and clinical application.

Western medicine proved to be beneficial in tumor diagnosis and treatment, but it induces serious adverse reactions. Traditional Chinese medicine may also improve patients’ quality
of life. However, the lack of an effective evaluation system restricts the development of traditional Chinese medicine. The integration of Western and traditional Chinese medicine may work synergistically to become the new mainstream treatment for cancer patients.

Elemene, a natural lipid-soluble plant drug extracted from Curcuma Wenyujin, has been widely used as an effective anticancer drug. The active ingredients of an elemene injection are β-elemene, γ-elemene, α-elemene, and the excipients include granulesten, cholesterol, alcohol, disodium hydrogen phosphate and sodium dihydrogen phosphate. The β-elemene has been proven to be the main active ingredient. Thus far, it is known that elemene has a broad-spectrum anticancer effect with bioapplications in bone cancer, lung cancer, ovarian cancer, and so on. It is considered to be safe when compared with other traditional chemotherapy drugs due to its low toxicity level to the normal cells.

In recent years, several systematic investigations have been carried out on antitumor mechanisms of elemene. Clinical studies have shown a significant role in inhibiting tumor growth. Combined treatment of elemene injection, radiotherapy, and chemotherapy may enhance the effectiveness of the treatment, and mitigate several serious adverse reactions. Elemene injection combined with radiotherapy in the treatment of lung cancer with brain metastases has already been adopted in clinical settings. Its effectiveness and safety have already been reported from clinical trials; however, a systematic review, according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA), which can provide guidance for this combination therapy regimen is lacking. Hence, this meta-analysis aims to provide an evidence of effectiveness and safety for the clinical use of elemene injection combined with radiotherapy in the treatment of lung cancer with brain metastases.

2. Methods

2.1. Searching strategies

Published studies were retrieved from 7 databases, including EMBASE, PubMed, Cochrane Library, China Knowledge Resource Integrated Database (CNKI), Chinese Scientific Journal Database (VIP), Chinese Biomedical Database (CBM), and Wanfang Database (from established to July 2016). The initial search was designed to find all trials using the following search phrases either separately or in combination, “lung cancer,” “brain metastases,” “elemene injection,” “radiotherapy.” All randomized controlled trials (RCTs) were reviewed as the systematic literature review in Chinese and English. Ethical approval was not required, as this study is a meta-analysis of published studies.

2.2. Inclusion criteria

2.2.1. Types of study. Randomized controlled clinical trials focused on the treatment of lung cancer with brain metastases using elemene injection and radiotherapy were selected, regardless of the absolute or relative risk. All randomized controlled trials (RCTs) with complete and precise data were included.

2.2.2. Exclusion criteria. We excluded RCTs of those had flawed data presentation, those had adopted different intervention measures, those had not provided precise data counting on response rate, and those had participants with any comorbidity. Non-RCTs were excluded from this meta-analysis.

2.2.3. Types of participants. All patients were 18 years old and above, and histologically or cytologically confirmed non-small cell lung cancer and brain metastases documented by magnetic resonance imaging or computed tomography scan.

2.2.4. Types of intervention. This meta-analysis included all randomized trials involving lung cancer with brain metastases undergoing chemotherapy and radiotherapy. The intervention treatment group combined elemene injection with radiotherapy, and the control group was treated with only radiotherapy.

2.3. Outcome measurement

Two of the reviewers independently extracted data on objective tumor response, reductions in radiotherapy toxicity, and improved or stable performance status. The outcomes were evaluated using Objective Response Rate (ORR), Karnofsky Performance Status (KPS) score improvement rate, and the symptoms improvement rate. The ORR was calculated as the number of patients presenting any response (partial response along with complete response) divided by the total number of patients in each treatment group. The KPS score improvement rate was calculated as the number of patients whose KPS scores increased by more than 10 points divided by the total number of patients in each treatment group. The common symptoms improvement rate was considered to assess the efficacy of therapeutic regimen. The incidence of adverse reactions was also systematically evaluated.

2.4. Data extraction

Data and information, including the name of first author, year of publication, the number of cases, demographic characteristics (age and sex), details of intervention, and outcomes were carefully extracted by 2 authors according to the predefined criteria.

2.5. Quality assessment

The methodological quality of each RCT was evaluated in terms of selective reporting, allocation concealment, random sequence generation, blinding of outcome, blinding of participants and personnel, incomplete outcome data, and other sources of bias based on the guidelines of the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0). The judgment was categorized as “Low risk,” “High risk,” or “Unclear risk” of bias. Two reviewers evaluated the studies that were matched with the pre-specified criteria for determining the effectiveness and safety of elemene injection combined with radiotherapy for the treatment of lung cancer with brain metastases independently to ensure validity. If there were disagreements between the 2 reviewers, a third researcher would resolve differences over the results of the studies. The Risk of bias graph and the Risk of bias summary were generated by using Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

2.6. Statistical analysis

The odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for each of the 4 outcomes: ORR; performance status; improvement of symptom; and the adverse reactions (bone marrow suppression and leukopenia). For the pooling analysis, Chi-square test was used to assess the existence of statistical heterogeneity. Fixed effect model was used when individual study
results showed homogeneity ($P > .1$ and $I^2 < 50\%$), otherwise, we used the random effect model ($P < .1$ and $I^2 > 50\%$) to estimate the summary OR. Egger test and Begg funnel plot were evaluated to assess publication bias. The level of significance was considered at $P < .05$. All statistical analyses were conducted with STATA (version 14.0; StataCorp LLC, Lakeway Drive, College Station, TX) and RevMan (version 5.3).

### 3. Results

The flow chart of the detailed searching steps for this meta-analysis is illustrated in Fig. 1. Twenty-one of all 170 screened clinical trials were matched with the inclusion criteria for determining the effectiveness and safety of elemene injection combined with radiotherapy in the treatment of lung cancer with brain metastases. Furthermore, after a thorough assessment, we excluded 10 RCTs: 5 trials were non-RCTs, 2 trials had data errors, and 3 trials adopted different intervention measures. Finally, we identified 11 studies that involved a total of 765 lung cancer patients with brain metastases. We assigned 383 patients who were treated with elemene injection and radiotherapy in the experimental group, and 382 patients who were treated with radiotherapy only in the control group. The main characteristics of all 11 included studies are given in Table 1.[13–23]

#### 3.1. Risk of bias

Figure 2 evaluates the risk of bias based on the quality of the included RCTs. Only 4 of 11 studies mentioned randomized grouping despite there was a lack of sufficient reporting of the randomization methods. In summary, 2 studies grouped the

---

**Table 1**

| Trials | Number of cases (T/C) | Mean age (T/C) | Sex (male/female) | Treatment | Control | Dosage | Outcome |
|--------|-----------------------|----------------|------------------|-----------|---------|--------|---------|
| Wu and Wang[13] | 32/30 | 54 | Unknown | Elemene injection +control | Radiotherapy | Radiotherapy (40 Gy/20f) elemene injection (300 mg/day) | AE |
| Hou and Lin[14] | 47/46 | 33–75 | 71/22 | Elemene injection +control | Radiotherapy | Radiotherapy (40 Gy/20f) elemene injection (400–600 mg/day) | ABS |
| Yin[15] | 8/11 | 43–70/ 46–69 | T:5/3 C:7/4 | Elemene injection +control | Radiotherapy | Radiotherapy (40 Gy/20f) elemene injection (20 mg/kg/day) | ABD |
| Liang[16] | 30/30 | 64.5/67.2 | T:18/12 C:16/14 | Elemene injection +control | Radiotherapy | Radiotherapy (40 Gy/20f) elemene injection (400–600 mg/day) | ABE |
| Wang and He[17] | 37/37 | 61 | Unknown | Elemene injection +control | Radiotherapy | Radiotherapy (40 Gy/20f) elemene injection (1000 mg/day) | AD |
| Zhang et al[18] | 43/43 | 51.6/51.4 | T:26/17 C:25/18 | Elemene injection +control | Radiotherapy | Radiotherapy (40 Gy/20f) elemene injection (600 mg/day) | A |
| Chi[19] | 30/30 | 62 | 43/18 | Elemene injection +control | Radiotherapy | Radiotherapy (40 Gy/20f) elemene injection (600 mg/day) | ABE |
| Guo and Su[20] | 18/18 | Unknown | T:13/5 C:11/7 | Elemene injection +control | Radiotherapy | Radiotherapy (30–40 Gy/10–20f) elemene injection (400 mg/day) | ABS |
| Lei[21] | 49/48 | 68.27 | 62/37 | Elemene injection +control | Radiotherapy | Radiotherapy (40 Gy/20f) elemene injection (600 mg/day) | AE |
| Tian and He[22] | 47/47 | 58.3/56.3 | T:31/16 C:28/19 | Elemene injection +control | Radiotherapy | Radiotherapy (40 Gy/20f) elemene injection (300–400 mg/day) | A |
| Tian and Du[23] | 42/42 | 46.7/46.2 | T:22/20 C:21/21 | Elemene injection +control | Radiotherapy | Radiotherapy (10 Gy/wk) elemene injection (unknown) | AB |

T: Treatment group; C: Control group.
A: objective response rate (ORR); B: KPS score improvement rate; S: Symptoms improvement rate.
D: Bone marrow suppression; E: Leukopenia.

---
patients on the basis of the hospital admission sequence and 4 studies used a random number table. None of the identified trials provided the details of the allocation concealment and blinding of outcome. All the included trials had a low risk of bias of incomplete outcome data. Other bias was evaluated as an unclear risk. However, we were unable to judge selective reporting bias because of the insufficient evidence provided by all of the identified trials. The summary of the authors’ judgments of the risk of bias is indicated in Fig. 3.

3.2. Objective response rate
All the identified studies for this meta-analysis reported ORR. The ORR (OR = 2.89, 95% CI 2.04–4.08, \(P < .00001\)) was higher in the elemene-based combination treatment group than those treated with radiotherapy alone, with no significant heterogeneity (\(\chi^2 = 3.89, P = .95, I^2 = 0\%\)) (Fig. 4).

3.3. Symptoms improvement rate
We identified 3 trials representing a total of 188 patients of lung cancer with brain metastases. Patients who were treated with elemene-based combinations (OR = 4.06, 95% CI 2.00–8.25, \(P = .0001\)) reported higher symptoms improvement rate than those patients who were treated with radiotherapy alone, with no significant heterogeneity (\(\chi^2 = 3.88, P = .99, I^2 = 0\%\)) (Fig. 5).

3.4. KPS score improvement rate
We identified 6 studies (350 patients) that reported the performance status of lung cancer patients with brain tumor metastases and treated with elemine-based combinations with radiotherapy or radiotherapy alone. The KPS score improvement rate of patients treated with elemene-based combinations with radiotherapy was higher than that of patients treated with radiotherapy alone (OR = 3.51, 95% CI 2.20–5.61, \(P < .00001\)), with no significant heterogeneity (\(\chi^2 = 2.59, P = .76, I^2 = 0\%\)) (Fig. 6).

3.5. Adverse reactions
3.5.1. Bone marrow suppression. Patients who received the combined treatment regimen (elemene injection along with radiotherapy) had a lower incidence of bone marrow suppression (OR = 0.27, 95% CI 0.11–0.68, \(P = .006\)) than that of patients treated with radiotherapy alone, with no statistical heterogeneity (\(\chi^2 = 1.64, P = .20, I^2 = 39\%\)). The forest plot of the incidence of bone marrow suppression is given in Fig. 7.
Figure 4. The forest plot of objective response rate.

Figure 5. The forest plot of symptoms improvement rate.

Figure 6. The forest plot of KPS score improvement rate.

Figure 7. The forest plot of the incidence of bone marrow suppression.
3.5.2. Leukopenia. Figure 8 illustrates that the patients who were treated with elemene injection combined with radiotherapy had a lower incidence of leukopenia (OR = 0.23, 95% CI 0.12–0.46, \( P < 0.00001 \)) than the patients treated with radiotherapy alone, with no substantial heterogeneity (\( \chi^2 = 0.74, \ P = .86, \ I^2 = 0\% \)).

3.6. Publication bias

There was lower publication bias according to the Begg funnel plot and the Egger test (\( P = .476 \)) in our study. Figure 9 indicates the funnel plot of the publication bias.

4. Discussion

The meta-analysis results from this study suggest that combining elemene injection with radiotherapy may improve tumor response, performance status, and symptoms of the disease, and reduce adverse effects (particularly bone marrow suppression and leukopenia) more than treatment with radiotherapy alone. We were unable to draw definitive conclusions, as most of the studies reviewed were of poor quality. Previous meta-analysis has proven poor methodological quality among the RCTs published in the Chinese and English journals\(^{[24,25]}\) and these scenario persisted in this meta-analysis. Although the findings of this meta-analysis may be restricted by the low quality of the trials identified in our systematic search, our findings proved that patients who were treated with elemene injection combined with radiotherapy had significant health benefits than those who were treated with radiotherapy alone.

The antitumor mechanisms of elemene contain the following elements: inhibiting the proliferation of tumor cells\(^{[26]}\); inducing apoptosis of tumor cells\(^{[27]}\); inhibition of tumor angiogenesis\(^{[28]}\); reversing multidrug resistance of tumor cells\(^{[29]}\); and radiosensitization.\(^{[30]}\) It should be noted that some previous published studies reported several adverse reactions caused by elemene injection, such as phlebitis, fever, pain, chest distress, and bleeding tendency.\(^{[31–34]}\) The lung cancer patients with brain metastases and being treated with elemene-based combinations reported higher symptoms and performance status improvement rate than those patients who were treated with the radiotherapy alone. For this reason, the elemene injection combined with radiotherapy appears to have a positive effect in improving the treatment of radiotherapy and the quality of life.

In this meta-analysis, the incidence of bone marrow suppression and leukopenia was found to be significantly decreased. However, the adverse effect of elemene injection was not reported in these included RCTs. Therefore, the safety of elemene injection could not be evaluated, and the potential adverse reactions need further investigation. In this regard, this study requires further clinical trials to report sufficient evidence on the safety of elemene injection in the treatment of lung cancer with brain metastases. This is the first meta-analysis, which evaluates the efficacy of elemene injection along with radiotherapy against radiotherapy alone in the treatment of lung cancer with brain metastases. Indeed, the elemene-based combination therapy had a better outcome than radiotherapy alone. However, it is noteworthy that the findings of this meta-analysis might be affected due to several limitations, such as insufficient reporting of the randomization methods used in the included trials, or the poor methodological
quality of the RCTs. Moreover, most of the identified trials included small sample sizes. Therefore, it is difficult to evaluate the long-term efficacy and safety of elemene-based combination treatment for lung cancer with brain metastases comprehensively and objectively. In addition, none of the identified trials provided the details of the allocation concealment and blinding of outcome, and we were also unable to judge selective reporting bias due to limited information provided by all the identified trials. Although the findings of this meta-analysis were limited by the low quality of the published studies, we identified insufficient reporting of the randomization methods. Therefore, we strongly recommend researchers to strictly follow the Cochrane handbook or Consolidated Standards of Reporting Trials (CONSORT). Complementary and alternative medicines require evidence-based standards for the demonstration of clinical effectiveness. Also, further study designs should consider standard based standards for the demonstration of clinical effectiveness. [35] Another, further study designs should consider standard based standards for the demonstration of clinical effectiveness.

5. Conclusion

Compared with radiotherapy alone, elemene injection combined with radiotherapy in the treatment of lung cancer with brain metastases may improve the treatment efficacy, alleviate the symptoms of patients, and reduce the adverse reactions induced by radiotherapy. However, additional randomized clinical trials with high methodological quality are required to generate conclusive results.

References

[1] Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87–108.
[2] Chen WQ, Zheng RS, Zhang SW, et al. Report of cancer incidence and mortality in China, 2012. China Cancer 2016;25:1–8.
[3] Chen WQ, Zhang SW, Zhou XN. Estimation and projection of lung cancer incidence and mortality in China. Chin J Lung Cancer 2010;13:488–93.
[4] Hoskin PJ, Bradley M. Radiotherapy for brain metastases. Clin Oncol (R Coll Radiol) 2001;13:91–4.
[5] Liang T, Geng P. The present situation and prospect of treatment of traditional Chinese and Western medicine treatment of brain metastasis of lung cancer. Chin Commun Doctors 2014;30:9–10.
[6] Efferth T, Li PC, Konkimalla VS, et al. From traditional Chinese medicine to rational cancer therapy. Trends Mol Med 2007;13:353–61.
[7] Hsiao WL, Liu L. The role of traditional Chinese herbal medicines in cancer therapy: from TCM theory to mechanistic insights. Planta Med 2010;76:1118–31.
[8] Eisenberg DM, Davis RB, Etter SL, et al. Trends in alternative medicine use in the United States, 1990–1997: results of a follow-up national survey. JAMA 1998;280:1569–75.
[9] Liu J, Zhang Y, Qu J, et al. Beta-elemene-induced autophagy protects human gastric cancer cells from undergoing apoptosis. BMC Cancer 2011;11:183.
[10] Tang XH, Qin SK, Xie T. Status and progress of basic researches of elemene injection for anti-tumor. Chin Clin Oncol 2010;15:266–73.
[11] Tan W, Lu J, Huang M, et al. Anti-cancer natural products isolated from Chinese medicinal herbs. Chin Med 2011;6:27.
[12] Xie T, Li CL, Wang SL, et al. The basic research progress of elemene liposome, a natural targeted drug. Chin J Integr Trad West Med 2014;34:507–12.
[13] Wu M, Wang SY. The clinical research on lung cancer patients with brain metastasis treated by elemene emulsion. J Med Forum 2006;27:80–1.
[14] Hou W, Lin HS. Clinical study of elemene injection combined with radiotherapy in treatment for non-small cell lung cancer patient with brain metastasis. China Cancer 2007;16:1021–2.
[15] Yin HM. The Short Term Efficacy of (Elemene Injection Combined with Radiotherapy) in Treatment for Non-small Cell Lung Cancer Patients with Brain Metastasis [Master]. Jilin University, Changchun City, China: 2010.
[16] Jiang T. The Clinical Research on the Combination of Elemene Emulsion with Radiotherapy for Brain Metastasis of NSCLC [Master]. Beijing University of Chinese Medicine, Chaoyang District: 2011.
[17] Wang LM, He ZH. The clinical research on elemene emulsion in the treatment of lung cancer with brain metastasis. Med Inform 2014; 27:126–7.
[18] Zhang M, Yang FW, Yuan CJ. Effect of radiotherapy combined with elemene injection on lung cancer treatment. Chin J Biochem Pharm 2014;34:132–3.
[19] Chi HL. Clinical Study of Elemene Emulsion Combined With Radiotherapy in the Treatment of Non-small Cell Lung Cancer With Brain Metastasis Patients. Beijing: 2th Acute and Severe Experience Exchange Forum; December 18, 2015.
[20] Guo YW, Suo DF. Clinical observation on elemene injection combined with radiotherapy in the treatment of advanced lung cancer with brain metastasis. Chin Commun Doctors 2015;31:88–9.
[21] Lei ZY. Influence of elemene injection combined with radiotherapy on the levels of serum MMP-2 and -9 in patients with brain metastases from lung cancer. J Clin Med Pract 2015;19:21–3.
[22] Tian XY, He JJ. The clinical efficacy of elemene injection plus radiotherapy in the treatment of lung cancer with brain metastases and effect on serum MMP-2 and MMP-9. J Clin Med Pract 2015;19:948–5.
[23] Tian FQ, Du J. To observe the clinical curative effect of patients with elemene injection adjuvant treatment of brain metastases of lung cancer. Chin J Hosp Pharm 2016;36:395–7.
[24] Hewitt C, Hahn S, Torgerson DJ, et al. Adequacy and reporting of allocation concealment: review of recent trials published in four general medical journals. BMJ 2005;330:1037–8.
[25] He J, Du L, Liu G, et al. Quality assessment of reporting of randomization, allocation concealment, and blinding in traditional Chinese medicine RCTs: a review of 315 RCTs identified from 260 systematic reviews. Trials 2011;12:122.
[26] Que X. Research progress on the anti-tumor molecular mechanism of b-elemene. Pharm Clin Chin Mater Med 2015;6:61–4.
[27] Yu JW, Cheng B. The molecular mechanism research progress in apoptosis of tumor cells induced by elemene, China Pharm 2013;24:3348–50.
[28] Wang XM, Hu XJ. Research progress on the anti-tumor mechanism and reversal mechanism of drug resistance of b-elemene. Modern Oncol 2014;22:1711–4.
[29] Zhang YJ, Bao WL, Shi H. The current research status of b-elemene reversing multidrug resistance of tumor cells. J New Chin Med 2014;46:212–4.
[30] Liu MB. The enhancement of radiation sensitivity induced by b-elemene. Shenzen Journal of Integrated Traditional Chinese and Western Medicine 2015;25:173–5.
[31] Wang YJ, Zhang R, Wang WW. Six cases of adverse reactions induced by intravenous infusion of elemene injection. Chin J Hosp Pharm 2016;36:337–8.
[32] Wang WJ, Fang DS, Hua YH. Clinical analysis of new adverse reactions caused by the elemene injection. J Pract Oncol 2013;28:388–90.
[33] Tao XM, Gao WB. Prevention and treatment of adverse reactions caused by elemene injection. Adv Drug React J 2003;5:390–2.
[34] Wu XC, Huang JH, Zhou WS. The antitumor effect of elemene emulsion and the prevention and control of adverse reactions. Trad Chin Drug Res Clin Pharmacol 2004;15:70–2.
[35] Marwick C. Complementary, alternative therapies should face rigorous testing, IOM concludes. J Natl Cancer Inst 2005;97:255–6.