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Case Report

Successful maintenance therapy with oral etoposide following first-line therapy in an elderly woman with extensive-stage SCLC: a case report and literature review

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Abstract: Small cell lung cancer (SCLC) is a disease with poor prognosis whose outcome has not significantly been improved till now. Maintenance therapy as a therapeutic strategy was utilized in an attempt to delay cancer relapse, drug-resistance and improve survival. However, they develop rarely in elderly patients over 80-year old, and there are few reports about the information of maintenance therapy for elderly extensive-stage disease SCLC (ED-SCLC). Here, we present an 88-year old Chinese female patient who had tumors in left lower hilus pulmonis and multiple nodules in bilateral lungs, accompanying vertebral metastasis. SCLC was immunohistochemically confirmed after endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA). Maintenance oral etoposide was administered as maintenance therapy following first-line therapy with two cycles of cisplatin and etoposide chemotherapy, and recurrence was observed after 19 months of following-up. To our knowledge, the present case is the oldest ED-SCLC treated with maintenance chemotherapy.

Keywords: Maintenance therapy, oral, etoposide, SCLC

Introduction

Lung cancer is the leading cause of cancer death all around the world and SCLC accounts for about 10% to 15% of all lung cancer patients [1]. Approximately two-thirds of patients present with extensive-stage disease (ED) that has metastasized beyond chest and is incurable through the application of the current treatment method. ED-SCLC has a poor prognosis and its median overall survival (OS) remains to be 9-10 months with a one-year survival of about 40%. Four to six cycles of platinum-based chemotherapy may make tumor shrink dramatically, especially within the first few weeks of treatment. In spite of a high initial response rate to first-line therapy, the majority will die from relapse and drug-resistant disease within a few months of completing frontline therapy. It is difficult for patients to obtain similar therapeutic benefits from second-line therapy.

Recently, maintenance therapy has been a recommended treatment for patients with advanced non-small lung cancer (NSCLC), so as to improve progression-free survival (PFS) [2, 3]. But in current SCLC treatment guidelines, there is still no consensus on therapeutic strategy to support the recommendation for maintenance therapy. The purpose of treatment for elderly ED-SCLC patients is to manage related symptoms, avoid treatment-related toxicity, improve life quality and prolong survival. Therefore, applicable maintenance therapy with low toxicity is a wise and reasonable way to prolong PFS for elderly ED-SCLC patients. Through the treatment with maintenance oral etopside, a case of long-term PFS in elderly ED-SCLC patient with multiple lung and bone metastases is presented in the current report. Besides, written informed consent was obtained from the patient.

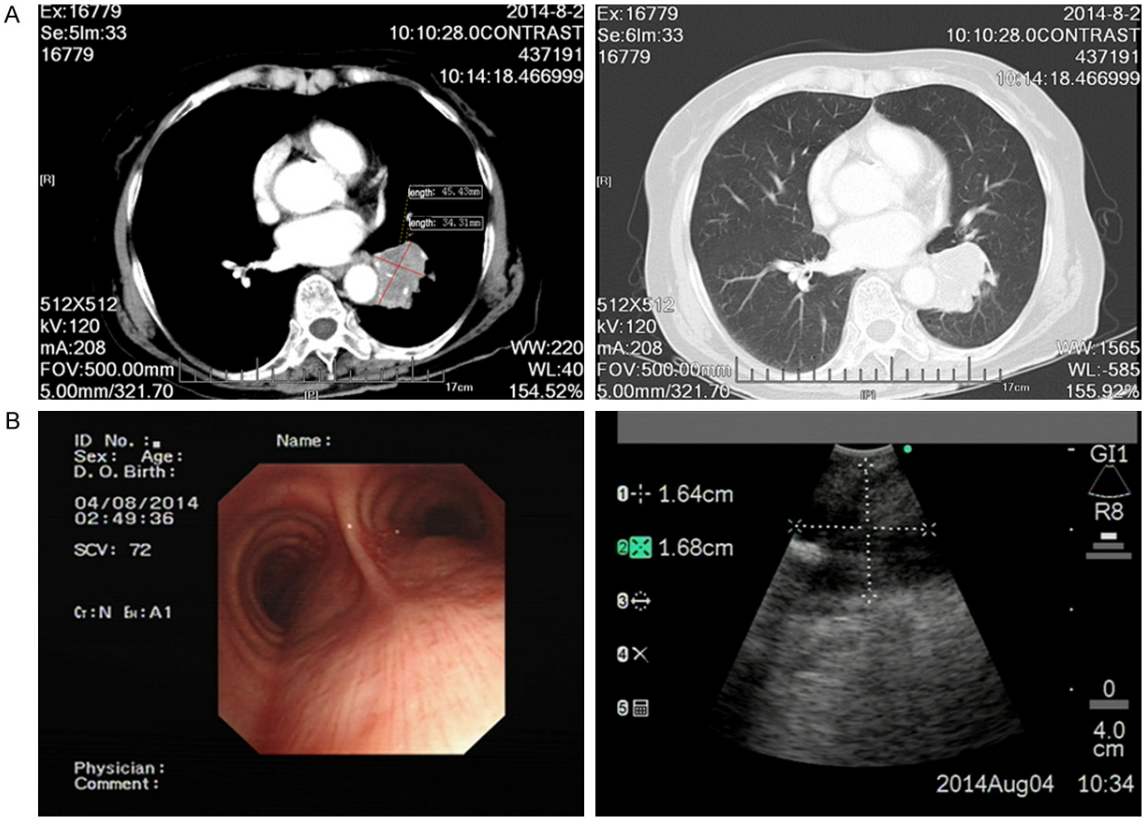

Figure 1. Prior to first-line chemotherapy, computerized tomography images of chest in August 2014 indicated an irregular lobulated mass shadow in left lower hilus pulmonis (A). In August 2014, images of endobronchial ultrasound-guided bronchoscopy (EBUS) examination, showed that accompanied by subcarinal (7) lymph node enlargement, the bronchus opening of the left lower lobe became narrow by a tumor (B).

Case report

In August 2014, an 88-year-old woman was admitted to our hospital due to cough, shortness of breath, intermittent fever (maximum 38.7°C) and lumbar spine pain. Having an Eastern Cooperative Oncology Group (ECOG) performance status of not more than 1, she was a housewife and non-smoker and had no family history of cancer. A computerized tomography (CT) scan of chest showed an irregular lobulated mass shadow in left lower hilus pulmonis, which was 45.43 mm × 34.31 mm in the largest cross section. In addition, the left lower bronchus became narrow and truncated and there were multiple nodules in bilateral lungs (**Figure 1A**). Furthermore, the endobronchial ultrasound-guided bronchoscopy (EBUS) examination revealed that accompanied by paratracheal (4R) and subcarinal (7) lymph node enlargement, the bronchus opening of the left lower lobe became narrow by a tumor (**Figure 1B**). The patient underwent EBUS-TBNA and histopathologic analysis showed small cell carcinoma (**Figure 2A**). Immunohistochemical staining showed positive staining for CK (**Figure 2B**), synaptophysin (SyN) (**Figure 2C**), chromogranin-A (CgA) (**Figure 2D**), neuron-specificenolase (NSE) and thyroid transcription factor 1 (TTF-1). Besides, magnetic resonance imaging (MRI) of lumbar vertebra displayed bone metastases in the first and second lumbar vertebral body (**Figure 3**). Through MRI of head, no metastasis was found in brain. Tumor markers found in serum involved carcinoembryonic antigen (CEA; 0.60 ng/mL), neuro-specific enolase (NSE; 34.82 ng/mL) and circulating cytokeration 19 fragments (CYFRA21-1; 5.65 ng/mL). Bone marrow and liver and kidney functions were normal.

The patient was diagnosed with ED-SCLC, bilateral lungs and bone metastases. In NCCN Guideline for Senior Adult Oncology, it has been

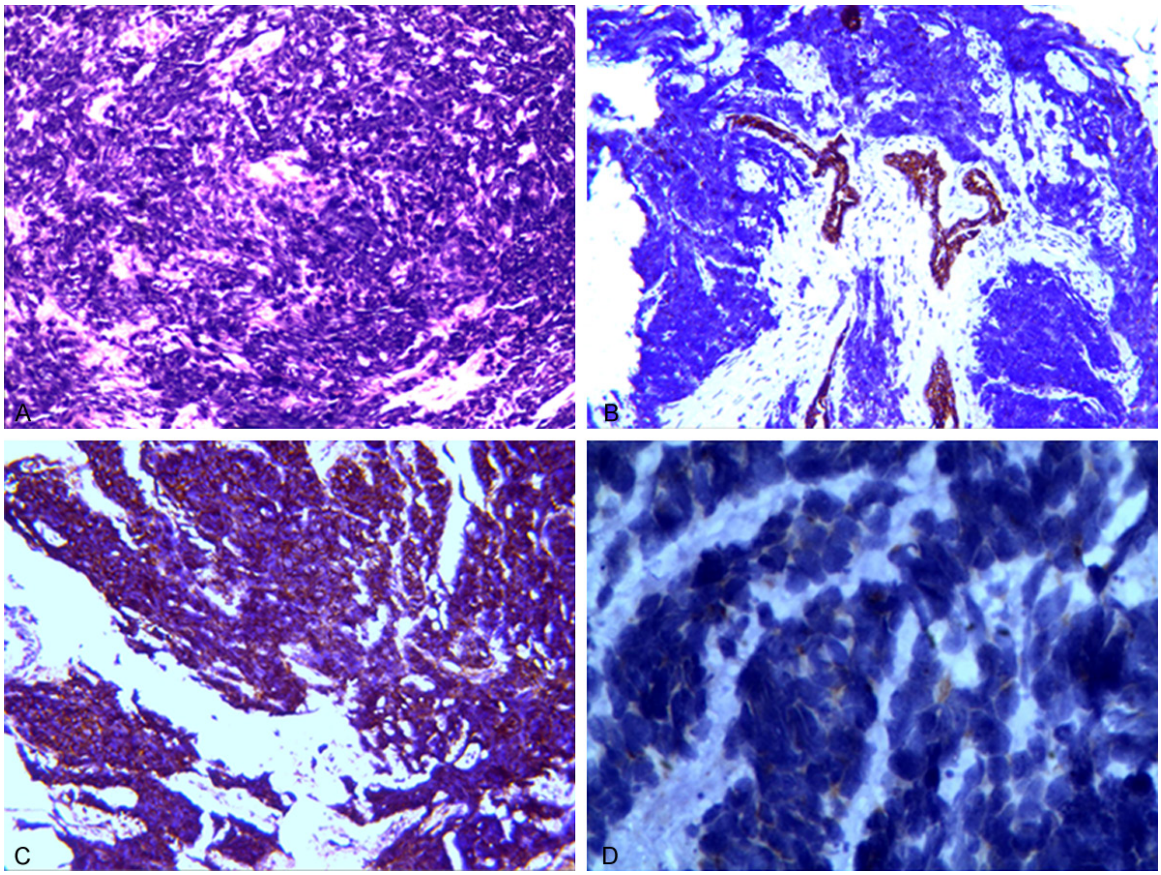

Figure 2. Histopathologic examination of the biopsy specimen revealed small cell carcinoma (A), immunohistochemical staining for CK (B), synaptophysin (C) and chromogranin-A (D).

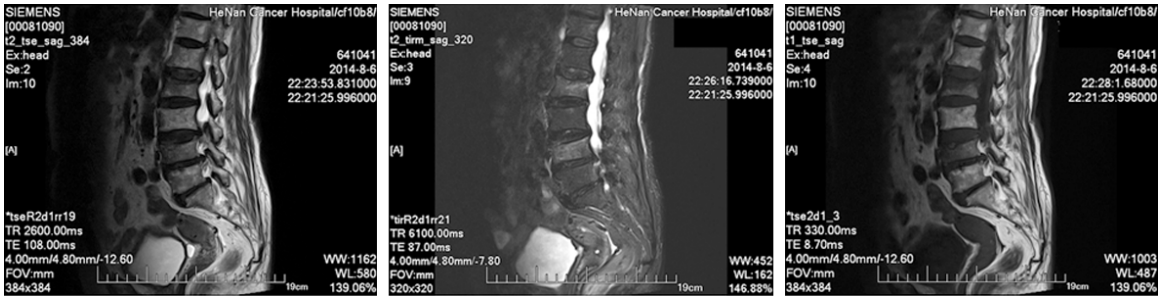

Figure 3. Magnetic resonance imaging (MRI) of lumbar vertebra showed bone metastases in the first and second lumbar vertebral body.

pointed out that advanced chronologic age has an adverse effect on the tolerance to treatment, however, individual patient's functional status is much more useful than age in guiding clinical decision-making. Randomized trials have indicated that in elderly patients with good performance status (0-2), less-intensive treatment is inferior to combined chemotherapy [4, 5]. Considering the declining renal function of aging patients, carboplatin plus etoposide seems to be an optimal selection [6]. Matsui *et al* published an essay detailing that targeting carboplatin to an area-under-the-curve (AUC) of 5 instead of 6 may be more reasonable in elderly population [7]. Therefore, chemotherapy was started with carboplatin (AUC 5) iv drip on day 1 and etoposide (80 mg/m^2) iv drip from day 1 to day 3 every 3 weeks in

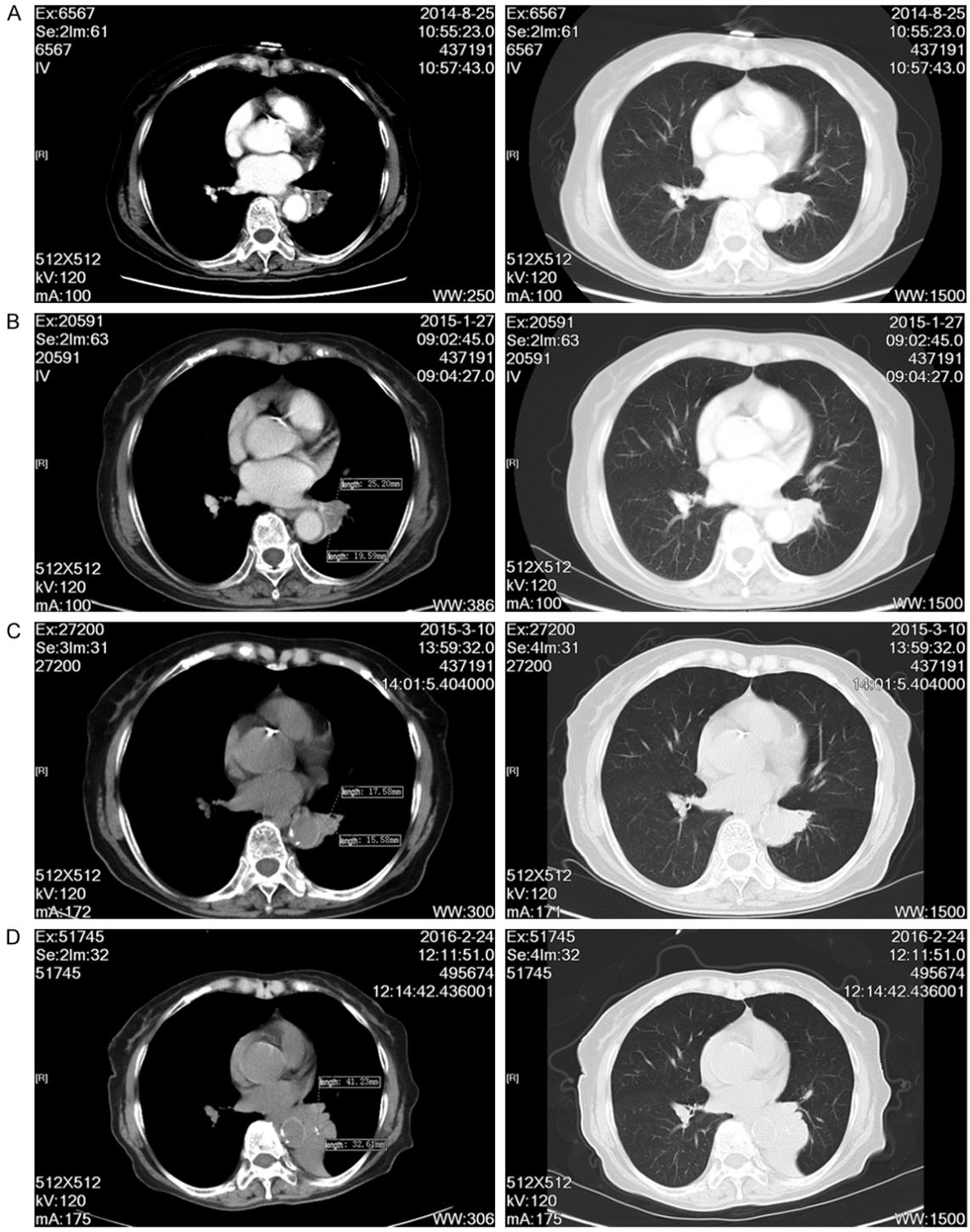

Figure 4. After one cycle of carboplatin plus etoposide chemotherapy, computerized tomography images of chest indicated that left lower hilus pulmonis tumor shrank significantly than before (A). After four cycles of maintenance lower dose oral etoposide, computerized tomography images of the chest showed that the tumor increased slightly (B). After the treatment with full dose of etoposide, the tumor shrank again (C). After 19-month progression-free survival, computerized tomography images of chest in February 24 indicated tumor progression (D).

August 2014. In addition, sodium ibandronate injection was administrated every 4 weeks to relieve metastatic bone pain. After the procedure, no fever, chill abdominal pain, constipation, diarrhea or jaundice was observed and side effects were limited to fatigue (grade 1),

nausea (grade 1) and myelosuppression (grade 1). After one cycle, primary symptoms had eased notably. In order to avoid excessive risks during treatment, a CT scan of chest was performed, which showed that left lower hilus pulmonis tumor significantly shrank to 24.19 mm × 17.37 mm and nodules in bilateral lungs remained unchanged (**Figure 4A**). According to Response Evaluated Criteria in Solid Tumors (RECIST version 1.1), partial remission (PR) was obtained after one cycle of chemotherapy for the old woman. Subsequently, she received the second cycle of chemotherapy.

Previous research has demonstrated that two cycles of full-intensity chemotherapy seemed to be acceptable in elderly or infirm patients, although this approach had not been compared with standard therapy directly [8]. After two cycles of chemotherapy with carboplatin plus etoposide, the old woman received 50 mg of maintenance oral etoposide from day 1 to day 14 every 4 weeks in September 2014. Taking lower organ function of the old woman into full consideration, etoposide dose was reduced by 20%. After four cycles of maintenance oral etoposide, a CT scan of chest revealed that the tumor increased slightly, but did not reach the progressive disease (PD) (**Figure 4B**). Every 4 weeks, etoposide dose was adjusted to 50 mg from day 1 day 21. After a month, a CT scan was performed again, which suggested that the tumor decreased when compared with the previous size (**Figure 4C**). Therefore, the old patient continued 50 mg of maintenance oral etoposide from day 1 to day 21 every 4 weeks. During the maintenance therapy, the patient was followed up through complete blood count, liver and renal function examination at every two weeks, as well as tumor marker and CT scan at every two months. After maintenance therapy, the evidence of recurrence has been detected as of 19 months on February 24, 2016 (**Figure 4D**).

Discussion

Characterized by a rapid doubling time, high growth fraction and early onset of distant metastases [9], SCLC has become one of the most frustrating malignancies that medical oncologists treat. A high objective response rate is guaranteed by combined chemotherapy, however PFS is disappointing and long-term OS usually remains to be less than 12 months [10, 11]. Through scores measured on life quality functional scales, patients treated with chemotherapy have a better life quality [12-14]. Strategies to improve SCLC outcome include dose intensification using higher doses of drugs or more frequently dosed with drugs aided by cytokine support, alternating non-cross-resistant regimens, adding new drugs in multi-agent combinations and maintenance therapy [15].

Following induction therapy, maintenance therapy in non-progressing patients was employed in SCLC patients by medical oncologists. However, the results obtained were contrasting, which made the interpretation of its role controversial. Among a number of interesting experiments, consolidation topotecan *vs.* observation was adopted in one of the largest phase III studies in ED-SCLC [13]. A significant 1.3-month improvement in PFS was observed in the topotecan group (3.6 *vs.* 2.6 months, $P<0.001$); but there was no improvement in median OS (9.3 *vs.* 8.9 months, $P=0.43$) and life quality were identified. Moreover, other studies have demonstrated that for SCLC patients who receive maintenance chemotherapy, no significant improvement in survival has been observed [16, 17] and even severe side effects or toxic death were caused by maintenance and consolidation therapy in some cases [18]. Fourteen randomized controlled trials (RCTs) were pooled in a meta-analysis and only chemotherapy was evaluated as maintenance treatment [19]. In absolute terms, maintenance chemotherapy respectively improved 1- and 2-year OS by 9% (from 30% to 39%) and 4% (from 10% to 14%); in addition, 1- and 2-year PFS were better with maintenance chemotherapy. In another meta-analysis, all approaches applied were evaluated as maintenance therapy, including 21 RCTs [18]. As a result, no significant advantage in OS or PFS was reported for maintenance therapy and side effects resulted in a higher percentage of patients stopping maintenance therapy. However, maintenance chemotherapy was found to significantly improve PFS in trials published after 2000 and extensive disease patients [14]. In recent years, an increasing attention has been paid to the possibility of immunotherapy and molecularly-targeted maintenance therapy for SCLC patients [20-22]. In a recent study, cellular immunotherapy (CIT) with autologous natural killer (NK), γδT and cytokine-induced killer

(CIK) cells as maintenance therapy for SCLC patients has been reported to improve OS (20 *vs.* 11.5 months, *P*=0.005) when compared with those to be followed up [20]. However, further multi-center randomized studies are needed.

The main purpose of maintenance therapy is to prolong stable disease status by adopting less toxic anticancer drugs. Therefore, a satisfactory clinical benefit from maintenance treatments cannot do with the application of highly toxic drugs. As a topoisomerase II inhibiting anticancer drug, etoposide can relegate cleaved nucleic acid molecules by forming and stabilizing topoisomerase II-etoposide-DNA ternary complex and thus increases topoisonerase II-mediated DNA breakage [23]. Etoposide activity is dose- and schedule-dependent and etoposide efficacy may be markedly improved by repeated drug administration [23-25]. Etoposide is commercially available in both intravenous and oral formulations. Compared with intravenous administration, oral etoposide bioavailability is about 60% and interpatient variability of systemic etoposide exposure is increased [26, 27]. Therefore, when applied by the oral formulation, approximately the double dose of etoposide is used to compensate for reduced uptake, which will result in similar levels of mean AUC to intravenous treatment [27]. Based on 50% bioavailability, oral etoposide has the same efficacy and lower toxicity as that with intravenous dosing in SCLC patients with dosing [28, 29]. Defined as metronomic chemotherapy, the administration of oral etoposide for a long time may overcome drug resistance via target tumor vasculature [30]. It has been considered that repeated exposure to low-dose metronomic treatment with oral etoposide may impair the anginogenic potential of endothelial cells and increase chemosensitivity [31]. Another single-institution experience result showed that followed by oral estoposide and bevacizumab maintenance treatment, cisplatin, etoposide and bevacizumab regimen appeared to be effective in terms of 9-month disease control rate in ED-SCLC patients [32]. Furthermore, maintenance oral etoposide was found to be an active drug in refractory testicular cancer, ovarian and germ-cell tumors [33-36].

After two cycles of carboplatin plus etoposide, maintenance oral etoposide was given to the patient, which improved PFS to 19 months. In the first four months, lower dose etoposide was used as maintenance chemotherapy for the old woman, which did not have obvious toxic effects. However, inadequate dose of etoposide made tumor increase slowly. After the treatment with full dose of etoposide, the tumor shrank again and stabilized up to 15 months and no significant drug-related complication occurred. Decision regarding treatment fitness should not be made upon age alone, which should result from a comprehensive assessment of the patient and the biology of the disease. The treatment strategy we proposed presented a good safety and effective profile.

The main drawback of oral etoposide is incomplete and variable bioavailability [23, 37]. As safety and efficacy were correlated with drugs AUC, oral etoposide administration may increase the variability in AUC and lead to a greater variability in safety and efficacy. El-Yazigi *et al.* investigated the optimisation of oral etoposide dose in elderly patients with non-Hodgkin's lymphoma [38]. By employing individual bioavailability data and therapeutic drug monitoring (TDM) approach, oral etoposide yielded good safety and efficacy and kept the toxicity at the level similar to that of intravenous administration simultaneously.

In conclusion, the case of a long-term elderly survivor of ED-SCLC is described in the present report. In spite of extra-chest metastasis at the initial diagnosis, the patient has 19-month PFS. Following first-line therapy with carboplatin plus etoposide, maintenance oral etoposide and good compliance contributed to the patient's long-term PFS in this case. Maintenance chemotherapy with oral etoposide may be a good choice for elderly ED-SCLC patients.

Disclosure of conflict of interest

None.

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