Clinical Case Report

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Anti-angiogenesis treatment in a patient with appendix metastasis of small cell lung cancer

A case report

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Abstract

Rationale: Small-cell lung cancer (SCLC) is a common pathological type of lung cancer, but appendiceal metastasis of SCLC was rare. At present, clinical studies on the maintenance therapy of SCLC have not reached a significant conclusion.

Patient concerns: We reported on a 52-year-old man who diagnosed as extensive stage SCLC with abdominal pain for 2 months, aggravated for 2 days.

Diagnoses: The patient was diagnosed with extensive-stage SCLC, relapsed with appendix metastasis after treatment by emergency abdominal surgery.

Interventions: The patient received systemic treatments, including surgery, bevacizumab in combination with chemotherapy and bevacizumab alone was continued as maintenance therapy.

Outcomes: The patient had an overall survival would more than 23 months, and he gained another 8 months of progression-free survival after first-line radiochemotherapy.

Lessons: Although SCLC appendix metastasis is rare, continuous anti-angiogenic therapy combined with bevacizumab maintenance therapy after surgical treatment can prolong survival.

Abbreviations: AA = acute appendicitis, Bev = bevacizumab, CT = computed tomography, ES-SCLC = extensive-stage small-cell lung cancer, NSCLC = nonsmall cell lung cancer, NSE = neuron-specific alcohol enolase, OS = overall survival, PFS = progression-free survival, SCLC = small cell lung cancer, VCAM = vascular cell adhesion molecule, VEGF = vascular endothelial growth factor.

Keywords: anti-angiogenic, appendix metastasis, maintenance, SCLC

1. Introduction

In 2018, 2.1 million new cases of lung cancer were reported worldwide, accounting for 11.6% of all cancer cases,[1] of which small-cell lung cancer (SCLC) accounted for 10% to 11% of all lung cancer cases[2]; the age of onset is concentrated in the 60 to 80-year age group. In China, the estimated number of lung cancer cases in 2015 was 733,000, with SCLC accounting for approximately 100,000 people.[3] Almost all SCLC cases were related to smoking.[4]

The 5-year survival rate of SCLC remains <7%,[5,6] and most people die within 1 year of diagnosis. Unlike non-SCLC (NSCLC), there are still no targeted drugs for SCLC. In addition, compared with NSCLC, SCLC has the characteristics of faster doubling time and extensive metastasis in the early stage. Therefore, 60% to 70% of SCLCs are diagnosed with an extensive stage. SCLC metastasis occurs in the liver, lymph nodes, brain, and other body parts, but its occurrence in the rectum,[7] stomach,[8] and appendix is rare. Currently, only 8 cases of appendiceal metastasis have been reported in the English literature. At the same time, current clinical studies reported that the treatment of extensive-stage (ES) SCLC (ES-SCLC) with bevacizumab combined with chemotherapy or single-agent maintenance therapy did not prolong the survival time, but only extended the progression-free survival (PFS) time for 1 month.[7,8] Here, we report our experience of using bevacizumab combined with chemotherapy and bevacizumab alone as continuous maintenance therapy for a man with SCLC who achieved an 8-month PFS following second-line therapy.

2. Case presentation

In October 2016, a 52-year-old man visited a previous hospital because of coughing, and computed tomography (CT) revealed a

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This case report was written following the CARE guidelines. Informed consent was obtained from the patient and his family for publication of this case report and accompanying images.

The authors have no conflicts of interest to disclose.

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left hilar mass with left pleural effusion. Tumor cells were found in the pleural effusions, and a diagnosis of SCLC was made based on pathological test results. Subsequently, the patient underwent concurrent chemoradiotherapy. The patient started chemotherapy with etoposide and cisplatin for 4 cycles (etoposide 100 mg d1–3, cisplatin 20 mg d1–5, for 21 days, body surface area, 1.86 m^2). Evaluation of the lesion according to the response evaluation criteria in solid tumors (RECIST) 1.1 criteria after completing 4 cycles of chemotherapy revealed partial response. The lesions in the left lung were treated with radiotherapy (radiation was administered in large fields at 1.8 Gy/fraction, 5 days/week for a total dose of 50.4 Gy), followed by 2 cycles of chemotherapy. After that, the patient was not followed up with regular chest examinations. Since early September 2017, the patient experienced intermittent abdominal pain; however, the position of the pain was not fixed, and thus, no treatment was initiated. On November 7, the patient's abdominal pain further worsened, but it was relieved after oral administration of amoxicillin. However, on November 9, the abdominal pain aggravated again and transferred to the lower right abdomen. Emergency CT examination of the lower abdomen at our hospital revealed that the appendix and its wall had thickened, dense liquid was visible in the cavity, and surrounding tissues could not be clearly observed. A small amount of fluid exudate was also observed, and thus, acute suppurative appendicitis was suspected (Fig. 1A, B). Laparoscopic exploration and appendectomy were performed. The appendix was found to have significant congestion and edema. The perforation of the appendix was approximately 2 mm. The appendix was excised and sent for pathological examination. The pathological diagnosis was malignant endocrine tumors of the appendix, and immunohistochemical test results were as follows: AE/AE3 (+), CEA (+++), CK8 (-), CD56 (+++), Syn (+), and CgA (+), and Ki67 was approximately 90% (Fig. 1). The pathological test results also reported the source of small-cell neuroendocrine cancer lung. After postoperative recovery, the patient received chemotherapy with irinotecan (CPT-11, 120 mg intravenous infusion on days 1 and 8) and carboplatin (CBP, 300 mg intravenous infusion on day 1) along with bevacizumab (5 mg/kg intravenous infusion on day 1). Three days before chemotherapy, a Chinese herbal decoction of Banxia Xiexin decoction was administered to prevent irinotecan-induced diarrhea, and thus, the patient did not have diarrhea. After 4 cycles of chemotherapy, the neuron-specific enolase (NSE) levels returned to normal (Fig. 2), and a chest CT scan revealed that the lesions and pleural effusion were significantly reduced (Fig. 3D). The lesion had a partial response according to RECIST 1.1 criteria. However, the patient developed grade 2 myelosuppression according to the CTCAE 5.0 criteria. Considering that the patient previously received 10 cycles of chemotherapy and radiotherapy, the chemotherapy drugs were discontinued, but bevacizumab (5 mg/kg, intravenous infusion on day 1, repeated every 3 weeks) was maintained. After completing 6 cycles of bevacizumab maintenance therapy, the disease was stable, and NSE levels fluctuated above normal (Fig. 2). At the 8-month follow-up, no evidence of recurrence was noted; however, the patient died of severe lung infection in September 2018.

3. Discussion

Acute appendicitis (AA) is a common disease worldwide; however, the primary tumor and its metastasis of the appendix are rare.[9] AA caused by appendiceal metastasis from lung cancer is rare, and only 7 cases of appendiceal metastasis of SCLC have been reported.[10] Appendiceal metastases from SCLC are usually diagnosed only after AA develops. Only 1 case of appendiceal metastasis from SCLC was detected on fluorodeoxyglucose position emission tomography, and 1 case was detected by ultrasonographic examination that was useful for detecting appendiceal metastasis.[9,11] The optimal therapy for appendiceal metastasis is appendectomy.[10] Because of the low incidence of

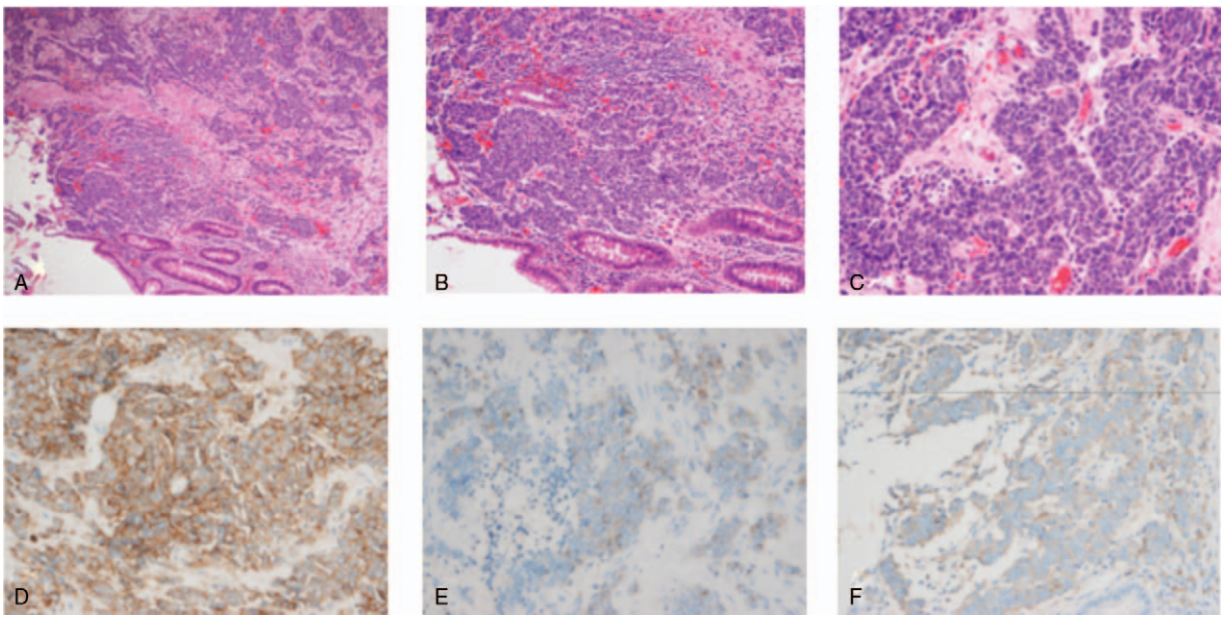

Figure 1. Hematoxylin and eosin staining of resection specimen shows small-cell lung cancer in A, B, and C (magnification ×10, HE × 20 and HE × 40); Immunohistochemistry for CD56, CgA and Syn in a serial section of the same specimen in (D–F), and syn shows positive staining predominantly in the tumor tissue (magnification ×40).

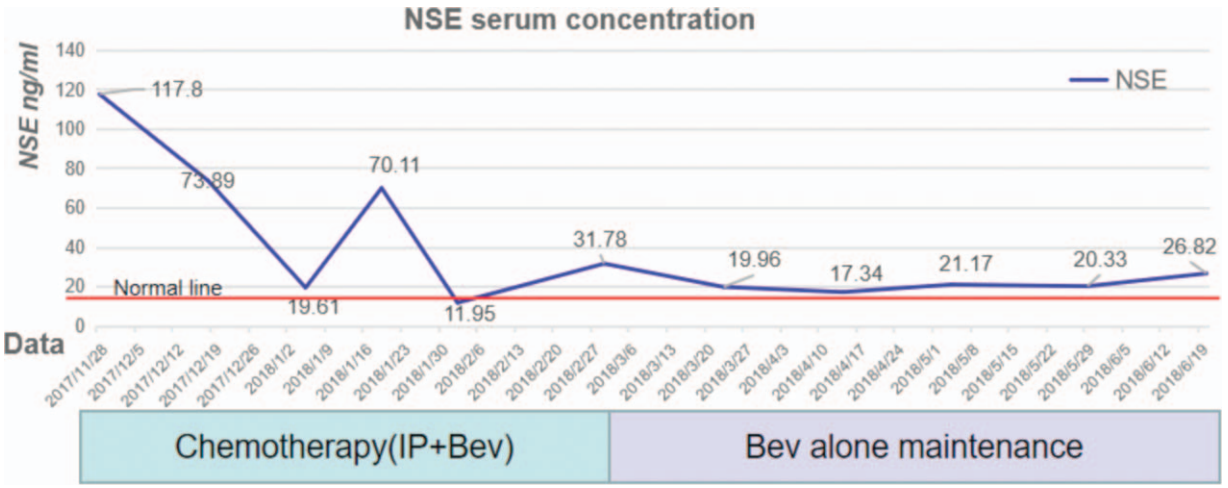

Figure 2. Treatment progress. Transition and progression of tumor marker levels. November 28, 2017: Initiation of chemotherapy (IP and Bev) administration. The neuron-specific alcohol enolase (NSE) serum concentration immediately declined to below the reference value following initiation of therapy. March 2017: Initiated bevacizumab alone maintenance administration. However, the NSE serum concentration was 31.78 ng/mL, which exceeded the reference value (16.3 ng/mL). Thereafter, no evident new lesions were observed, and the NSE serum concentration was maintained between 19.96 and 26.82 ng/mL, marginally greater than the reference value.

appendiceal metastasis, its pathogenesis remains unclear, and follow-up treatment remains similar to the treatment of ES-SCLC. It is important to note that since 1970, there has been no significant breakthrough in the treatment of ES-SCLC, and the current treatment remains based on chemotherapy.

3.1. First-line chemotherapy for ES-SCLC

The current standard chemotherapy for ES-SCLC patients include regimens of etoposide along with cisplatin or carboplatin (VP-16+DDP/CBP, EP/EC) and irinotecan along with cisplatin or carboplatin (CPT-11+DDP/CBP, IP/IC). The response rate is

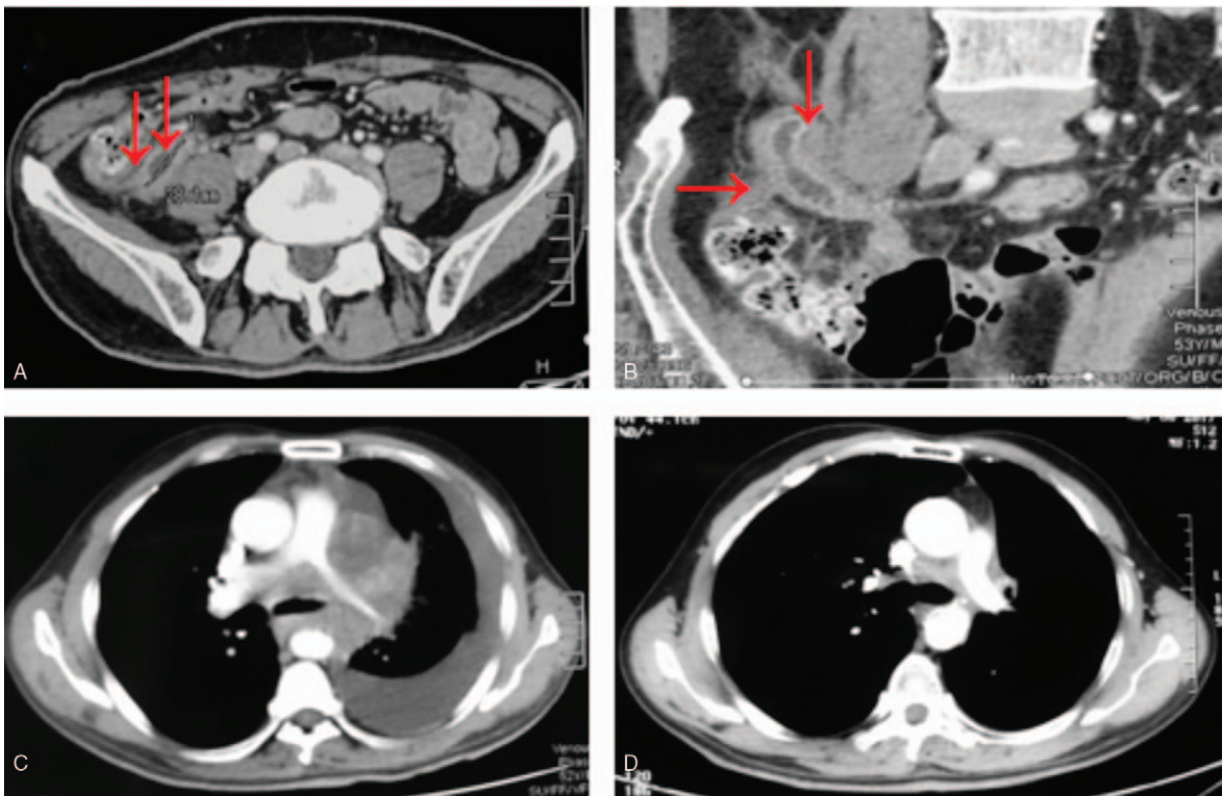

Figure 3. Abdominal CT showed obvious thickening of the appendix with thickening of the appendix wall and liquid density in the appendix cavity. The surrounding tissue was not clear, and a small amount of liquid exudation (A, B) was seen around the ileocecal area; left lung mass, mediastinum metastasis combined with left pleural effusion (C); left lung lesions reached PR after chemotherapy combined with anti-angiogenic therapy (D).

50% to 80%, and the median survival time is approximately 9 to 12 months.[12] Many other chemotherapy combinations have been evaluated for patients with ES-SCLC, with little consistent evidence of benefit when compared with the EP regimen. The IP regimen initially demonstrated certain advantages in clinical trials. In a Japanese phase III trial, irinotecan along with cisplatin was compared with etoposide along with cisplatin in patients with ES-SCLC; the trial enrolled patients with no prior radiotherapy and chemotherapy or surgery. The primary endpoint of the trail was overall survival (OS). In total, 154 patients were enrolled, with 77 assigned to receive four 4-week cycles of irinotecan and cisplatin (CPT-11 65 mg/m^2 intravenous infusion on days 1, 8, and 15, repeated every 3 weeks; DDP 60 mg/m^2 intravenous infusion on day 1) and 77 assigned to receive four 3-week cycles of etoposide and cisplatin (VP-16 100 mg/m^2 intravenous infusion on days 1 through 3 and DDP 80 mg/m^2 intravenous infusion on day 1). The results revealed that the complete response rate was 2.6% in the IP group, and the overall response rate was 84.4%. The complete response rate and overall response rate in the EP group were 9.1% and 67.5%, respectively. The overall response rate of the IP group was significantly higher than that of the EP group ($P=0.02$). The 1- and 2-year OS rates of the IP group were 58.4% and 19.5%, respectively. However, the 1- and 2-year OS rates of the EP group were only 37.7% and 5.2%, respectively. The risk of death in the IP group compared with that in the EP group was 0.60 (95% confidence interval, 0.43–0.83). The most frequent toxic effect in both the groups was myelosuppression, with EP being more common; moreover, the incidence of grade 3 to 4 delayed diarrhea in the IP group was significantly higher than that in the EP group. All cases of grade 1 to 4 delayed diarrhea in the IP group occurred during the first and second cycles of treatment, and thus, loperamide hydrochloride or a Chinese herbal decoction such as hange-shashin-to (Banxia Xiexin decoction) was administered to ameliorate the diarrhea at the discretion of the attending physicians to prevent irinotecan-induced diarrhea.[12] Banxia Xiexin decoction is a 7-herb Chinese medicine formula comprising Rhizoma Pinelliae, Radix Scutellariae, Rhizoma Zingiberis, Radix Codonopsis, Radix Glycyrrhizae, Rhizoma Coptidis, and Fructus Jujubae. The decoction has been proven to prevent delayed diarrhea in clinical and basic studies. Therefore, the regimen of irinotecan and cisplatin is an attractive option for patients with ES-SCLC who have a good performance status.

Hermes et al[13] conducted a phase III randomized, double-blind, controlled clinical trial enrolling 220 patients with initial treatment of ES-SCLC. The patients were randomly assigned to receive either carboplatin [area under the curve (AUC), 4.0 mg/mL/min] and irinotecan (175 mg/m^2) intravenously both on day 1 or carboplatin and etoposide (120 mg/m^2/d1–5) orally. The results revealed that the median survival time was 8.5 months for the IC group compared with 7.1 months for the EC group, and the 1-year survival rates were 34% and 24% for IC and EC, respectively. Furthermore, 18 patients had complete response in the IC group compared with 7 patients in the EC group ($P=.02$). The results also supported the IC regimen as the standard chemotherapy regimen for ES-SCLC and demonstrated that the treatment could prolong survival in patients with ES-SCLC. However, the incidence of grade 3 to 4 diarrhea in the IC group was significantly higher than that in the EC group ($P=.003$). Similarly, a meta-analysis in 2017 suggested that the incidence of grade 3 to 4 anemia, leukopenia, neutropenia, thrombocytopenia, and granule-deficient fever in the IP regimen was lower than that in the EP group, whereas the incidence of grade 3 to 4 nausea, vomiting, diarrhea, anorexia, and fatigue in the IC group was higher than that in the EP group, and the OS and 1-year survival rates of the IP group were higher than those of the EP group.

Phase III clinical studies in the United States revealed no significant difference in OS between IP and EP for ES-SCLC.[14,15] A meta-analysis of the OS time and median progression time of the EP and IP protocols showed that IP not only improved the survival time but also increased the toxicity.[16] Thus, the NCCN guidelines still recommend etoposide combined with platinum as the standard protocol for the treatment of SCLC. After 4 to 6 cycles of standard treatment, consolidation and maintenance chemotherapies showed some sustained remission; however, instead of improving survival, it dramatically increased cumulative toxicity.[17] Moreover, a meta-analysis revealed that the maintenance chemotherapy did not prolong survival.[18]

3.2. Bevacizumab as an antiangiogenic therapy for ES-SCLC

Angiogenesis factor is an important proangiogenic factor that promotes the formation of pathological blood vessels and tumorigenesis.[19] Most tumors, including lung cancer, have elevated vascular endothelial growth factor (VEGF) levels. The number of new blood vessels and the expression of VEGF in SCLC are elevated, which may be associated with poor prognosis in small cells.[20,21] Increased internal hypoxia of the tumor promotes neovascularization by inducing VEGF factor binding to the VEGF receptor (VEGFR), thereby activating the VEGF pathway. Similarly, fibroblast growth factor and angiopoietin-2 continue to stimulate angiogenesis. VEGF and VEGFR inhibitors have achieved satisfactory clinical results. SCLC angiogenesis is a key to SCLC metastasis.[20] Therefore, anti-angiogenic therapy for SCLC patients may be an ideal therapeutic strategy.

Bevacizumab, a human monoclonal antibody against VEGF, is currently used to treat tumors such as lung adenocarcinoma,[22] colorectal cancer,[23] and ovarian cancer.[24] However, clinical trials of bevacizumab for treating SCLC revealed that the treatment did not prolong survival. The ECOG3501 trial validated the efficacy and safety of the combination of IP and bevacizumab. The trial group revealed a PFS of 4.7 months and OS of 10.9 months, which were similar to those observed in other clinical trials of the same chemotherapy regimen without bevacizumab. At the same time, vascular cell adhesion molecule can be a poor prognostic factor for survival.[25]

A phase II SALUTE study validated the safety and efficacy of standard chemotherapy combined with bevacizumab as the first-line treatment of ES-SCLC. A total of 102 patients were enrolled, including 52 in the experimental group. The treatment regimen was cisplatin (25 mg/m^2 intravenous infusion on days 1–3) or CBP (AUC, 4.0 mg/mL/min, intravenous infusion on day 1) combined with etoposide (100 mg/m^2 intravenous infusion on days 1–3) and bevacizumab (10 mg/kg intravenous infusion on day 1) repeated every 3 weeks for 4 cycles. In the control group, 50 patients were treated with the same chemotherapy regimen and placebo. The primary endpoint was PFS. The PFS of the test and control groups were 5.5 and 4.4 months, respectively, whereas the OS were 9.4 and 10.3 months, respectively. Bevacizumab could improve PFS; however, it did not make sense to prolong the survival period.[8] The CALGB 30306 study

also validated the efficacy of the IP regimen in combination with bevacizumab for treating ES-SCLC. The trial did not achieve the primary endpoint of a PFS of 7.0 months and an OS of 11.6 months. A subgroup analysis showed that patients with hypertension during the treatment were more likely to benefit from bevacizumab treatment.[26]

3.3. Bevacizumab as maintenance therapy for SCLC

A phase II clinical trial in the United States enrolled 51 patients who received IP combined with bevacizumab [CPT-11 60 mg/m^2 intravenous infusion on days 1, 8, and 15; CBP AUC, 4.0 mg/(mL/min) intravenous infusion on days 1; Bev 10 mg/kg intravenous infusion on days 1 and 15, repeated every 4 weeks] regimen chemotherapy. After 6 cycles of combination therapy, the disease did not progress, and the patients could tolerate continued treatment; thus, bevacizumab maintenance therapy was continued. The main study endpoint was time-to-progression (TTP). At the end of OS, the results showed that 84% of patients achieved an objective response, and 37% of patients received bevacizumab maintenance therapy (the median 3 cycle). The median TTP was 9.13 months, and the median survival time was 12.1 months. Furthermore, 51% of patients survived for >1 year, and 14% survived for 2 years. Bevacizumab maintenance treatment-related toxicity comprised anemia, thrombocytopenia, diarrhea, dehydration, hyperglycemia, etc. The trial showed that bevacizumab combined with IP regimen could improve chemotherapy effectiveness but could also increase toxicity.[27] The France phase II-III study IFCT-0802 compared chemotherapy with EP alone and EP combined with bevacizumab (7.5 mg/kg) followed by bevacizumab maintenance therapy. The results differed from those of other clinical trials, that is, patients enrolled in the group were first treated with induction chemotherapy to reduce the risk of bleeding caused by bevacizumab and then were randomly assigned to the chemotherapy alone group (n = 37) or the chemotherapy and bevacizumab group (n = 37). There were no significant differences in PFS and OS between the 2 groups. Moreover, bevacizumab (7.5 mg/kg) along with chemotherapy and maintenance therapy after induction did not improve outcomes in ES-SCLC patients, and serum vascular VEGF and soluble VEGF receptor titers were not related to the prognosis of the 2 groups.[28]

A phase III clinical study in Italy compared the efficacy of EP and EP in combination with bevacizumab (7.5 mg/kg) for treating newly diagnosed ES-SCLC. The primary endpoint was OS. Overall, 204 patients who were not previously treated with systemic therapy were enrolled. Among 96 patients enrolled for chemotherapy and bevacizumab, 41 (42%) continued bevacizumab therapy beyond the sixth cycle of therapy, with an average of 4 cycles of bevacizumab maintenance therapy. The conclusion was that chemotherapy and bevacizumab did not significantly improve survival of patients with ES-SCLC, although it did prolong PFS.[7]

In summary, appendiceal metastasis from SCLC is rare, and the optimal therapy for appendiceal metastasis is appendectomy, which is similar to the treatment of ES-SCLC. The IP regimen can prolong the survival of ES-SCLC in patients with good physical status. Banxia Xiexin decoction can prevent delayed diarrhea caused by irinotecan. Bevacizumab combined with chemotherapy and bevacizumab maintenance therapy for ES-SCLC can improve the objective response rate and prolong PFS with an acceptable toxicity profile. Although most current clinical trials did not report that bevacizumab combined with EP regimen could improve the survival of ES-SCLC, most results of phase II or III clinical trials showed that IP combined with bevacizumab and bevacizumab maintenance therapy prolonged PFS and could also prolong OS. In our case, IC regimen combined with bevacizumab and bevacizumab maintenance therapy led to a PFS of 10 months, demonstrating a good trend of bevacizumab maintenance therapy for ES-SCLC. However, the specific efficacy of the treatment needs to be confirmed by more phase III clinical trials.

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Author contributions

Peng Xue and Ningjun Wang contributed equally to this work. All authors contributed toward drafting, and revising the paper and agree to be accountable for all aspects of the work.
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Writing – review & editing: Yun MAO, Shijie ZHU.

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