

# Advances in antiangiogenic treatment of small-cell lung cancer

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**Abstract:** Small-cell lung cancer (SCLC), a poorly differentiated neuroendocrine malignancy, has a rapid growth rate, strong aggressiveness, early metastases, and poor prognosis. Angiogenesis greatly contributes to the metastatic process of SCLC, which has a higher vascularization compared with non-small-cell lung cancer (NSCLC). SCLC might constitute an ideal malignancy for assessing new antiangiogenic drugs and therapeutic strategies. Combining bevacizumab with paclitaxel has therapeutic benefits in chemoresistant, relapsed SCLC. The cisplatin–etoposide and bevacizumab combination, as the first-line treatment for extensive-stage SCLC, can improve progression-free survival (PFS), with an acceptable toxicity profile. Ziv-aflibercept combined with topotecan is promising for platinum-refractory SCLC. Chemotherapy combined with thalidomide cannot prolong survival. Maintenance sunitinib of 37.5 mg/day in extensive-stage SCLC patients following induction chemotherapy with platinum/etoposide improves median PFS by 1.6 months. Serum angiopoietin-2 concentrations and vascular endothelial growth factor levels correlate with poor prognosis. Bevacizumab, ziv-aflibercept, and sunitinib are worthy of further evaluation. Thalidomide, sorafenib, pomalidomide, and cediranib may not be suitable for SCLC.

**Keywords:** small-cell lung cancer, bevacizumab, sunitinib antiangiogenic therapy

## Introduction

Small-cell lung cancer (SCLC), a malignancy with high aggressiveness and poor differentiation, shows an alarming average overall 5-year survival rate below 10%.<sup>1</sup> Even after robust responses to initial chemotherapy and radiation, it recurs easily, and there are no standard therapeutic strategies for relapsed SCLC.<sup>2</sup> SCLC grows more rapidly and metastasizes at a very fast rate. Cancer angiogenesis, reflected by the number of formed microvessels, and the related modulators, are markedly associated with the metastatic potential of non-small-cell lung cancer (NSCLC) after surgery.<sup>3</sup> Combining bevacizumab with carboplatin/paclitaxel has an acceptable toxicity profile, with significant therapeutic benefits in Chinese individuals suffering from advanced non-squamous NSCLC.<sup>4</sup> Bevacizumab has received approval from both the American and Chinese authorities for use as a first-line therapeutic drug in advanced NSCLC.

Angiogenesis may be a very early process in vivo which is due to the imbalance between angiogenic and antiangiogenic mediators. Angiogenesis involved in multiple, overlapping pathways and mechanisms. Hypoxia in the growing tumor can stimulate angiogenesis and activate the vascular endothelial growth factor (VEGF) pathway by inducing the production of VEGFs that bind to VEGF receptors (VEGFRs). Fibroblast growth factor (FGF) and angiopoietin-2 also sustain the continuous activation of angiogenesis. The inhibitors of VEGF and VEGFR, matrix metalloproteinase, and other target genes or proteins begin to show clinical efficacy. Since angiogenic

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pathways are critical to SCLC metastasis,<sup>5</sup> SCLC may be an ideal malignancy suitable for assessing new antiangiogenic drugs and therapeutic strategies. There is no established role for antiangiogenic therapy in SCLC, and the challenge is to understand whether treatment effects in a subpopulation are lost among unselected patients. It is crucial to identify predictive biomarkers for antiangiogenic therapy. This review focuses on the advances of antiangiogenic treatment in SCLC.

## Bevacizumab

Bevacizumab is a monoclonal antibody targeting VEGF; it inhibits angiogenesis in malignant tumors, including NSCLC and SCLC. It is the drug that has demonstrated an impact on overall survival (OS) in the first-line treatment and maintenance therapy for stage IV non-squamous NSCLC.<sup>4</sup> In extensive-stage SCLC, bevacizumab is the most studied antiangiogenic drug. Topotecan is one of the main drugs used for the second-line treatment of relapsed SCLC. An open-label multicenter single-arm phase II study showed that administration of bevacizumab and oral topotecan improved the 3-month progression-free survival (PFS) (65%) compared with the historical control (50%), but did not meet the predefined criteria. Fifty patients were enrolled, and median PFS was 6.24 months for the sensitive subgroup and 2.91 months for the resistant subgroup. None of the patients achieved complete response, and the objective response rate (ORR) was 16%. The topotecan-bevacizumab combination in treating relapsed SCLC was promising and needs to be further evaluated.<sup>6</sup> Administration of bevacizumab plus irinotecan for the treatment of relapsed, resistant SCLC, for which only 32 patients were enrolled and 28 of them were eligible for evaluation, demonstrates promising efficacy and low toxicity compared to historical controls, and further investigation is warranted.<sup>7</sup> Addition of bevacizumab to paclitaxel was found to be feasible and effective in chemoresistant, relapsed SCLC as salvage treatment, although no improvement in outcome was found in relapsed chemosensitive SCLC patients.<sup>8,9</sup> A study assessed SCLC patients who relapsed within 3 months of first-line chemotherapy. Treatment with a combination of paclitaxel and bevacizumab for 28-day cycles showed an overall ORR of 20% and a disease control rate (DCR) of 36.7%. In addition, median response duration, PFS, and OS were 2.5, 2.7, and 6.3 months, respectively. Grade 3 and 4 side effects only included neutropenia, diarrhea, and fatigue. This combination therefore represents a suitable substitute treatment, which should be imperatively evaluated in relapsed, chemoresistant SCLC patients.<sup>9</sup> The French Cooperative Thoracic Intergroup (IFCT)-0802 study showed

that bevacizumab administration following induction chemotherapy in extensive-stage SCLC does not ameliorate patient response or PFS.<sup>10</sup> The dose of bevacizumab administered for the IFCT-0802 study was 7.5 mg/kg, not the routine dose of 15 mg/kg. A single-institution experience showed that cisplatin–etoposide (EP) combined with bevacizumab before oral etoposide administration and bevacizumab maintenance therapy shows likely more efficacy and is relatively safe in extensive-stage SCLC patients.<sup>11</sup> Another randomized phase II study of the addition of bevacizumab to cisplatin or carboplatin plus etoposide (EC) for the treatment of extensive-stage SCLC achieved the similar results which only improved PFS but not OS with an acceptable toxicity profile.<sup>12</sup> Irinotecan plus carboplatin can also be used in the treatment of extensive-stage SCLC. A phase II trial assessed the effect of irinotecan, carboplatin, and bevacizumab in the treatment of these patients. Fifty-one patients were enrolled and four patients were unassessable. ORR was 84%, median time to progression (TTP) 9.13 months, and median OS 12.1 months. No significant bleeding occurred. Larger randomized trials comparing irinotecan, carboplatin, and bevacizumab with chemotherapy alone are further warranted.<sup>13</sup> EP, as a monotherapy or used in combination with bevacizumab as first-line therapy for extensive-stage SCLC, was assessed in a multicenter, phase III randomized trial. All the subjects were randomized to arm A (EP/EC) or B (same chemotherapy combined with bevacizumab). Interestingly, addition of bevacizumab improved PFS (5.7 vs 6.7 months,  $P=0.030$ ) with tolerable toxic effects, while there was no statistical difference in OS, the primary endpoint.<sup>14</sup> Tracheoesophageal fistulae are rare but serious complications in lung and esophageal cancers. Medication warnings and a change in bevacizumab is labeling, due to combination of bevacizumab and chemoradiotherapy is associated with a relatively high incidence of tracheoesophageal fistulae formation in limited stage SCLC.<sup>15</sup> Bevacizumab combined chemotherapy in SCLC can improve PFS not OS, but the evidence is weak and most of them are derived from phase II trials. Although toxicity is controllable, tracheoesophageal fistulae should be paid more attention, especially with chemoradiotherapy.

## Ziv-aflibercept

Ziv-aflibercept comprises high-affinity binding domains from VEGFR1 and VEGFR2 fused to the fragment crystallizable (Fc) region of human immunoglobulin (IgG)1. It recognizes placental growth factor, VEGF-A and VEGF-B, and essentially removes these ligands.<sup>16,17</sup> It is used in the USA to treat patients with metastasized colorectal cancer.<sup>18</sup> One hundred and eighty-nine patients were enrolled in a phase II trial,

assessing SCLC subjects administered platinum with weekly topotecan alone and in combination with ziv-aflibercept.<sup>17</sup> The patients were treated every 3 weeks and classified according to platinum sensitivity. Three-month PFS was markedly ameliorated by ziv-aflibercept in platinum-refractory disease unlike the sensitive type. The DCR was increased in the combination group compared with those treated with topotecan as monotherapy, regardless of the platinum sensitivity status. The OS of patients who received topotecan combined with ziv-aflibercept was similar to that of those administered topotecan. An addition of ziv-aflibercept led to more grades 3–5 toxicities. Ziv-aflibercept combined with topotecan is a promising therapeutic option for platinum-refractory SCLC. Toxicity and efficacy need to be in a balance, and a further phase III trial is warranted.

## Endostar

Folkman et al first identified endostatin, the 20 kDa internal fragment of the carboxy terminus of collagen XVIII, in 1997. Endostar, a novel recombinant human endostatin expressed and purified in *Escherichia coli*, is one of the most effective angiogenesis inhibitors.<sup>19</sup> A phase II trial assessing EP and endostar for extensive-stage SCLC demonstrated slightly higher PFS and OS compared with historical controls treated with this chemotherapeutic regimen alone, with acceptable side effects.<sup>20</sup> Addition of endostar to EC in the treatment of extensive-stage SCLC was evaluated for efficacy and safety. One hundred and forty patients with extensive-stage SCLC were randomized to EC alone or EC combined endostar, with endostar administered thereafter until intolerable toxic effects or progression. Median PFS were 6.4 and 5.9 months in the EC–endostar combination and EC groups, respectively. The ORRs of combination group and EC as monotherapy group were 75.4% and 66.7%, respectively ( $P=0.348$ ). Median OS rates were similar for the two groups. There were no significant differences between the two groups in the incidence of both nonhematological and grade 3–4 hematological toxicities.<sup>21</sup> An addition of endostar to EC may not be suitable for the treatment of extensive-stage SCLC as this regimen did not improve OS, PFS, and ORR.

## Thalidomide

Thalidomide, though a drug prescribed to treat morning sickness in pregnant women, induced birth defects, but now it is an effective drug for cancer treatment through antiangiogenesis and potent immunomodulatory effects. Mall et al reported a long-term survival in an SCLC patient after administration of thalidomide and combination chemotherapy.<sup>22</sup> A phase II study assessing thalidomide

as maintenance therapy in extensive-stage SCLC after response to chemotherapy showed that thalidomide has acceptable side effects.<sup>23</sup> Thalidomide combined chemotherapy for maintenance in SCLC was also assessed in 25 chemotherapy-naive SCLC patients; interestingly, chemotherapy-related toxicity was not increased, with an ORR of 68%. Median PFS and OS were 8.3 and 10.1 months, respectively.<sup>24</sup> A phase III trial evaluating thalidomide for advanced SCLC after chemotherapy showed that this drug did not significantly improve patient survival. However, some benefits were found for patients with a performance status of 1 or 2.<sup>25</sup> In addition, 119 patients received two cycles of etoposide, cisplatin, cyclophosphamide, and 4'-epidoxorubicin (PCDE). Responders to this treatment were randomly divided for the administration of four additional PCDE cycles in combination with thalidomide and placebo, respectively. After two treatment cycles, an ORR of 81.5% was obtained, with 92 individuals randomly divided into placebo (n=43) and thalidomide (n=49) groups.<sup>25</sup> Another study assessing thalidomide/chemotherapy for antiangiogenic effects in SCLC also demonstrated that combining thalidomide with chemotherapy showed no improvement in survival but promoted the occurrence of thrombotic events.<sup>26</sup> Several known inflammatory and angiogenic markers were assessed, and none were specific to patients who benefited from thalidomide treatment.<sup>27</sup> Patients with a performance status of 1 or 2 may be suitable to use thalidomide, but it needs a prospective randomized controlled study to verify.

## Sunitinib

Sunitinib (SU11248) shows a direct anticancer effect via KIT (CD117) and inhibits angiogenesis through VEGFR, and platelet-derived growth factor receptor- $\beta$  (PDGFR- $\beta$ ).<sup>28</sup> A phase II clinical trial, in which the treatment regimen consisted of a 6-week cycle of sunitinib (50 mg daily for 4 weeks followed by 2 weeks off) in relapsed or refractory SCLC, showed that the majority of subjects tolerated the therapy, with short median PFS. With the currently used regimen, further assessment may not be useful for sunitinib.<sup>29</sup> Nine patients were registered in a single-arm phase II study of sunitinib, with a loading dose of 150 mg followed by 37.5 mg/day, in patients with SCLC who were either chemo naive (extensive disease) or have a “sensitive” relapse. DCR at 8 weeks was achieved in two patients, and one toxic-related death was reported due to bronchial hemorrhage. The study was closed because of low accrual, with only 9 of required 48 patients accrued.<sup>30</sup> Cancer and Leukemia Group B (CALGB) (Alliance) 30504 is a phase II trial, which evaluated sunitinib vs placebo for maintenance in individuals suffering from extensive-stage

SCLC following induction chemotherapy with platinum/etoposide.<sup>31</sup> Patients without progression were assigned to sunitinib and placebo groups and treated until progression. One hundred and forty-four SCLC patients were enrolled, of which 138 were subjected to chemotherapy. A total of 95 subjects were randomized, among which 85 were administered maintenance treatment with sunitinib (n=44) or placebo (n=41). Most prominent grade 3 adverse events (AEs) were fatigue (19%), leukopenia (7%), reduced neutrophil counts (14%), and reduced platelet count (7%) in the sunitinib group; fatigue (10%) was also found as AE in the placebo group. Grade 4 AEs include pancreatitis, hypocalcemia, elevated lipase (in the same individual), and gastrointestinal hemorrhage (n=1) in sunitinib-treated patients; hypernatremia (n=1) and thrombocytopenia (n=1) were found in the placebo group. Median PFS in maintenance therapy were 3.7 and 2.1 months, respectively, for the treatment and placebo groups, respectively; median OS were similar in the two groups.<sup>31</sup> A trend toward PFS and OS improvement was found in individuals treated with prophylactic cranial irradiation and sunitinib.<sup>32</sup> This should not alter the current standard of care as only a small absolute improvement in median PFS (1.6 months) was observed over placebo;<sup>33,34</sup> however, we believe that maintenance sunitinib of 37.5 mg/day met its primary endpoint with an improvement in median PFS of 1.6 months over placebo and toxicity included grade 3 fatigue in 19%. Maintenance sunitinib is safe and should be further evaluated in phase III studies. Sunitinib maintenance following irinotecan and carboplatin as the first-line treatment for patients with extensive-stage SCLC was evaluated in a phase II study. Patients with stable disease or responding disease proceeded to sunitinib monotherapy (25 mg orally daily) until disease progression or unacceptable toxicity. Thirty-four patients were enrolled, of which 17 were initiated with sunitinib monotherapy. One-year OS was 54%, and median TTP was 7.6 months. Grade 3/4 toxicity was rare during sunitinib monotherapy.<sup>35</sup> Further study of sunitinib therapy in a randomized phase III trial maintenance would be appropriate. Improving the outcome of patients with extensive-stage SCLC following induction chemotherapy might need prophylactic cranial irradiation and thoracic radiotherapy, as well as maintenance systemic treatment.<sup>32</sup>

## Sorafenib

Sorafenib is a multi-tyrosine kinase inhibitor (TKI) targeting Raf-kinase, PDGFR, and VEGFR. The effect of EP plus concurrent and sequential sorafenib on untreated extensive-stage SCLC was evaluated.<sup>36</sup> The patients received four

cycles of EP chemotherapy concurrently with sorafenib. Those without progression after four cycles were further administered a higher sorafenib dose as maintenance for  $\leq 12$  months. The regimen of EP combined sorafenib at current dose levels has significant toxicity, and the efficacy results have been disappointing.<sup>36</sup> The suitable dose of sorafenib combined EP is still unknown, and toxicity should be paid more attention.

## Pomalidomide

Pomalidomide has been shown to have potent antiangiogenic and tumoricidal effects as they inhibit proangiogenic factors, VEGF, and basic FGF. The maximum-tolerated dose (MTD), safety, and clinical benefit of pomalidomide combined with EP chemotherapy in treatment-naive patients with extensive-stage SCLC were evaluated in a phase I/IIA study. Twenty-two patients received one or more doses of the study medication. Pomalidomide at the MTD of 4 mg/day plus standard EP seems safe, but the addition of pomalidomide does not seem to improve the therapeutic index based on the ORR (31.8%) and median OS (49.6 weeks).<sup>37</sup> Pomalidomide may be not a promising drug in SCLC.

## Cediranib

Cediranib, an oral TKI of VEGFR-1, VEGFR-2, VEGFR-3, and c-kit, has antitumor activity in recurrent epithelial ovarian cancer, fallopian tube cancer, and peritoneal cancer with predictable toxicities.<sup>38</sup> A phase II trial assessing the safety and efficacy of cediranib was carried out in refractory or recurrent SCLC. A dose of 45 mg of cediranib was employed daily (12 patients), and later this was decreased to 30 mg daily for subsequent individuals due to intolerance. Of the twenty-five patients enrolled, nine showed stable disease, and none had partial response. Median PFS and OS were 2 and 6 months, respectively. Cediranib treatment resulted in no objective response.<sup>39</sup> Cediranib is not worth for further study in SCLC.

## Vandetanib

Vandetanib is an inhibitor of VEGFR and epidermal growth factor receptor (EGFR). Vandetanib (300 mg/day) or matched placebo maintenance therapy in SCLC patients responding to induction chemotherapy was evaluated in a double-blind randomized phase II trial. One hundred and seven patients were accrued, and the results revealed that vandetanib had more toxicity, including asymptomatic corrected QT interval prolongation, and required more dose modifications for rash and gastrointestinal toxicity. Vandetanib failed

to demonstrate efficacy as maintenance therapy in these patients.<sup>40</sup> Another randomized, double-blind, phase II trial of platinum therapy plus etoposide with or without concurrent vandetanib (100 mg daily) in patients with previously untreated SCLC for up to total four cycles showed that the addition of vandetanib did not improve outcomes, and that nonhematologic toxicity increased; the trial included 74 patients of which 33 were randomized to each arm.<sup>41</sup> Vandetanib may not be a promising drug in SCLC.

## Nintedanib

Nintedanib, a potent, oral angiokinase inhibitor that targets the proangiogenic pathways mediated by VEGFR1–3, FGF receptor (FGFR) 1–3, and PDGFR- $\alpha$  and  $\beta$ , has demonstrated a survival benefit in combination with docetaxel vs docetaxel alone in previously treated lung adenocarcinoma. A phase II study was conducted to evaluate the efficacy and safety of nintedanib with 200 mg BID daily in a 4-week cycle until progression or intolerable toxicity in relapsed SCLC patients. Twenty-four patients were enrolled, who exhibited progression after one or two prior chemotherapy or chemo/radiotherapy, of which 22 patients were evaluable for response. Nintedanib exhibited only limited activity and showed the following results: ORR 5%, median PFS 1.0 month, and OS 9.8 months with grade 3 hepatic enzyme elevation occurring at 23%.<sup>42</sup>

## Prognostic markers

VEGF is critical to the angiogenic process, and its circulating levels could be a further prognostic marker in SCLC. Angiopoietin-2 is an angiogenesis-related cytokine.<sup>43</sup> Ustuner et al<sup>44</sup> reported that reduced circulating levels of VEGF represent an independent prognostic factor for SCLC. Investigation of VEGF and its related receptors for predicting the chemotherapeutic response seems worthless.<sup>44</sup> Research by Lucchi showed that microvessel amounts and VEGF expression markedly affect patient survival, and constitute independent prognostic factors.<sup>3</sup> Serum VEGF and soluble VEGFR titers failed to identify predictive biomarkers. High baseline circulating angiopoietin-2 levels are correlated with worse OS and constitute an independent predictor of OS.<sup>45</sup>

## Conclusion

None of the antiangiogenic drugs were approved in the treatment of SCLC because the data were not sufficient and satisfactory, despite some drugs were promising. The use of angiogenesis inhibitors in extensive SCLC is still restricted. Bevacizumab combined with platinum/etoposide

for extensive-stage SCLC can improve PFS and requires further studies. Maintenance sunitinib of 37.5 mg/day in extensive-stage SCLC is safe and deserves further evaluation in phase III studies. Ziv-aflibercept combined with topotecan is promising for platinum-refractory SCLC. Chemotherapy combined with thalidomide, sorafenib, or pomalidomide may not be suitable for SCLC treatment. Cediranib failed to be effective in recurrent or refractory SCLC. Serum VEGF and angiopoietin-2 levels were both correlated with poor prognosis.

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## Disclosure

The authors report no conflicts of interest in this work.

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