



Bevacizumab in extensive-disease small cell lung cancer: the search continues

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The outcomes of extended stage small cell lung cancer (ED-SCLC) have remained unchanged over the past two decades, with a median survival of 10 months and a 2-year survival of 10%, despite addition of radiation therapy to certain subsets of patients (1). The combination chemotherapy with cisplatin and etoposide has remained unchanged since the late 1990's (2), despite testing multiple different agents, both cytotoxic and targeted agents.

Overexpression of VEGF has been noted in SCLC and has been associated with poor prognosis (3). Few phase II studies evaluating VEGF directed therapy have shown positive outcomes in SCLC, with the most notable trials of these are the ECOG E3501 study, LUN90 and the SALUTE trial. The ECOG 3501 (4) and LUN 90 (5) were single arm phase II studies which reported an overall response rate of 64% and 84% respectively. The overall survival (OS) in these two studies was 10.9 (ECOG 3501) and 12.1 months (LUN90). In the SALUTE trial (6), bevacizumab, when added to cisplatin and etoposide led to an improvement in progression free survival (PFS), but did not improve the OS, which was a secondary endpoint. Based on these studies, the GOIRC-AIFA trial was designed to assess the benefit of bevacizumab in ED-SCLC.

Tiseo (7) and colleagues reported results of the GOIRC-AIFA trial of cisplatin and etoposide with or without bevacizumab as first line therapy in ED-SCLC. This was a multicenter phase III study where 204 patients were randomly assigned to receive either cisplatin or carboplatin and etoposide for a maximum of six cycles or the same regimen with bevacizumab (7.5 mg/kg every three weekly). In the experimental arm, bevacizumab was continued as

maintenance therapy until progression or for a maximum of one year (18 cycles). The primary endpoint of the study was OS and secondary endpoints were PFS, complete and partial response rates. Although there was a statistically significant increase in the PFS by one month (5.7 *vs.* 6.7; HR 0.7; 95% CI, 0.54–0.97, *P*=0.030), the study failed to reach its primary endpoint of improvement in the OS. The median OS in chemotherapy arm was 8.9 months as compared to 9.8 months in the bevacizumab arm (HR 0.78; 95% CI, 0.58–1.06, *P*=0.113). As expected, hypertension was more commonly seen in the bevacizumab arm. Over 50% of patients in both the groups developed grade 3–5 adverse events. No statistically significant differences were seen in the non-hematological toxicities. The authors concluded that bevacizumab could be a potential treatment option.

A closer look at the study however reveals that there was no difference in response rates. Although statistically significant, the improvement in median PFS was only 1 month and the clinical relevance of this improvement is unclear. Moreover, we feel that while PFS is a valuable endpoint, especially in tumors where there are multiple second-line options, in SCLC, where second-line options are few, OS is probably a more clinically relevant endpoint.

Interestingly, sub group analysis revealed improved survival outcomes in men (HR 0.55) when compared to women (HR 1.5). Similar outcomes for gender were observed in the SALUTE trial (6) as well. The reason for worse outcomes in women is unclear. The current study shows that patients older than 65 years had better outcomes (HR 0.55) when compared to younger patients (HR 0.99). This is contrary to previous studies that showed worse

outcomes in older patients when treated with bevacizumab.

Several other trials have targeted the VEGF pathway in SCLC. The CALGB 30504 compared outcomes in patients with ED-SCLC who received chemotherapy (platinum, etoposide) followed by sunitinib maintenance (8). The PFS was 2.1 *vs.* 3.7 months on the sunitinib arm. The OS though improved from 6.9 to 9 months, was not statistically significant. Similarly, another study including vandetanib as maintenance therapy did not show any significant improvement in PFS or OS (9). In the light of these findings, the data seen with bevacizumab are not completely unexpected. Unfortunately, it appears that targeting the VEGF pathway, with bevacizumab or other agents is unlikely to significantly improve outcomes in ED-SCLC.

Disappointingly, the standard of care for front-line therapy in ED-SCLC remains a platinum-etoposide combination. However, with recent understanding of the biology of SCLC newer agents show promising outcomes. The checkpoint inhibitors (nivolumab and ipilimumab) and the antibody-drug conjugate against delta-like protein 3 (DLL3), rovalpituzumab tesirine are exciting novel agents being studied in the relapsed setting. If the preliminary results with these agents are confirmed, we may finally be able to actually improve the lives of these patients.

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References

1. Noda K, Nishiwaki Y, Kawahara M, et al. Irinotecan plus Cisplatin Compared with Etoposide plus Cisplatin for Extensive Small-Cell Lung Cancer. *N Engl J Med* 2002;346:85-91.
2. Evans WK, Shepherd FA, Feld R, et al. VP-16 and cisplatin as first-line therapy for small-cell lung cancer. *J Clin Oncol* 1985;3:1471-7.
3. Santarpia M, Daffinà MG, Karachaliou N, et al. Targeted drugs in small-cell lung cancer. *Transl Lung Cancer Res* 2016;5:51-70.
4. Horn L, Dahlberg SE, Sandler AB, et al. Phase II study of cisplatin plus etoposide and bevacizumab for previously untreated, extensive-stage small-cell lung cancer: Eastern Cooperative Oncology Group Study E3501. *J Clin Oncol* 2009;27:6006-11.
5. Spigel DR, Greco FA, Zubkus JD, et al. Phase II trial of irinotecan, carboplatin, and bevacizumab in the treatment of patients with extensive-stage small-cell lung cancer. *J Thorac Oncol* 2009;4:1555-60.
6. Spigel DR, Townley PM, Waterhouse DM, et al. Randomized phase II study of bevacizumab in combination with chemotherapy in previously untreated extensive-stage small-cell lung cancer: results from the SALUTE trial. *J Clin Oncol* 2011;29:2215-22.
7. Tiseo M, Boni L, Ambrosio F, et al. Italian, Multicenter, Phase III, Randomized Study of Cisplatin Plus Etoposide With or Without Bevacizumab as First-Line Treatment in Extensive-Disease Small-Cell Lung Cancer: The GOIRC-AIFA FARM6PMFJM Trial. *J Clin Oncol* 2017;35:1281-7.
8. Ready NE, Pang HH, Gu L, et al. Chemotherapy with or without maintenance sunitinib for untreated extensive-stage small-cell lung cancer: A randomized, double-blind, placebo-controlled phase II study—CALGB 30504 (Alliance). *J Clin Oncol* 2015;33:1660-5.
9. Arnold AM, Seymour L, Smylie M, et al. Phase II study of vandetanib or placebo in small-cell lung cancer patients after complete or partial response to induction chemotherapy with or without radiation therapy: National Cancer Institute of Canada Clinical Trials Group Study BR. 20. *J Clin Oncol* 2007;25:4278-84.

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