Editorial

Bevacizumab in small cell lung cancer

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Tiseo *et al*. published the clinical study evaluating the efficacy and the safety of bevacizumab a humanized monoclonal antibody directed against vascular endothelial growth factor (VEGF), combined with cisplatin and etoposide in first line chemotherapy for patients with extensive-disease (ED) of small-cell lung cancer (SCLC) (1). This is a multicenter, open-label, randomized controlled phase III trial supported by the Gruppo Oncologico Italiano di Ricerca Clinica (GOIRC)—Agenzia Italiana del Farmaco FARM6PMFJM. A total of 205 patients were randomly assigned receiving cisplatin and etoposide with or without bevacizumab. The primary end point was the overall survival (OS). At a median follow-up of 34.9 months, the median OS was improved in the bevacizumab arm (9.8 *vs*. 8.9 months; hazard ratio (HR) 0.78) with a 1-year survival rates of 37% and 25% respectively (HR 0.78; 95% CI: 0.58–1.06; P=0.113). In addition, the proportion of patients who reported an objective response was 58.4% for the "bevacizumab arm" and 55.3% for the control arm. Among the 96 patients treated with chemotherapy and bevacizumab, 41 patients (42%) continued bevacizumab beyond the preplanned sixth cycles of treatment with a median of four cycles of bevacizumab maintenance; the 65.8% of patients interrupted bevacizumab cause of disease progression. A statistically significant effect on the OS in whose patients receiving the bevacizumab-based maintenance was observed (HR 0.60; P=0.011) along with a well tolerance and as expected; only hypertension was the most frequent adverse event registered in the bevacizumab arm (grade 3 or 4, 6.3% *vs*. 1.0%; P=0.057).

Several studies showed the effect on survival of Bevacizumab in different tumors including non-small cell lung cancer (NSCLC) (2-5), where Bevacizumab is now approved in addition to standard platinum based chemotherapy or in maintenance in patients with NSCLC without driver-mutations (3-5). On the counterpart, in SCLC, the randomized trials showed poor results of the use of bevacizumab when added to standard chemotherapy (6).

In 2011, the first randomized PHASE II study of bevacizumab in previously untreated extensive-stage disease-SCLC (SALUTE) was performed (7). The primary end-point was the PFS. Patients were randomly assigned to receive bevacizumab or placebo plus chemotherapy. Although the median PFS was higher in the experimental group (based on bevacizumab) (5.5 *vs*. 4.4 month), this advantage was not translated into an increase of OS, which was longer in the control group (9.4 *vs*. 10.9 months). This trend was also confirmed into the IFCT-0802 trial which failed to show an improvement in survival with a bevacizumab-based treatment (8).

SCLC is a disease with higher tumor response rates supporting strongly the rationale of a maintenance approach in order to prolong the initial response to the standard chemotherapy due to the high tumor proliferation. The targeted therapy, such as bevacizumab, are considered an ideal approach for the maintenance treatment, as they exhibit a good toxicity profile allowing their administration for a long period. However, a recent meta-analysis was not

able to show any advantages in survival between with the use of novel targeted therapies as maintenance compared with placebo or no treatment in SCLC (9). In contrast, Tiseo *et al*. showed a significant effect on OS for whose patients receiving bevacizumab based-maintenance (1,10). Despite the possible bias related to that only patients who did not progress after chemotherapy had access to the bevacizumab based-maintenance, in our opinion, future randomized trials with specified end-points are needed to better define the role of the bevacizumab based-maintenance approach in the management of patients with SCLC who respond to first line therapy.

Unfortunately, up to now, no validated biomarkers predictive of response to bevacizumab are available in solid tumors (11-13); nevertheless some clinical reports suggested a possible role of hypertension related to bevacizumab in defining responders versus no-responders (14). Tiseo *et al*. (1) reported a preplanned subgroup analysis indicating a possible interaction between bevacizumab and sex in favors of female, but without any substantial indications or explanations. All together, these data support the clinical need to identify and/or validate surrogate clinical and/or biological markers of response to bevacizumab in future well designed/dedicated studies.

In conclusion, the addition of bevacizumab to standard first-line platinum-etoposide based-chemotherapy seems not to increase the outcome and the survival in SCLC. However, based on the Tiseo *et al*. report, further investigations focused on the biological drug based-maintenance approach in SCLC should be considered in the future. Moreover, in our opinion, the new trials based on the role of treatment maintenance in SCLC should also considered to clearly indicate as end-points the clinical and /or biomarkers of response/resistance to help the proper selection for the optimal candidates to biological drug based-maintenance therapy

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