Small cell lung cancer (SCLC) has become one of the most frustrating malignancies that medical oncologists treat. The majority of patients present with extensive-stage (ES) disease that has metastasized beyond the chest and is incurable with current treatment options. Most patients report significant symptoms including shortness of breath, fatigue, weakness, weight loss and pain that dramatically affect their quality of life. Four to six cycles of platinum-based chemotherapy rapidly improves these symptoms as 60-80% of patients will have dramatic shrinkage of tumor, typically within the first few weeks of treatment. Unfortunately, this response is rarely durable and the majority will relapse within a few months of completing frontline therapy. Second line therapy does not afford a similar therapeutic benefit and patients ultimately succumb to the disease. Despite decades of research, median survival remains 9-10 months with a 1-year survival of approximately 40%.

Continuation of platinum-based chemotherapy beyond 6 cycles has not improved survival or quality of life and toxicities including neuropathy and progressive asthenia have prohibited this approach. With the advent of newer, more tolerable anti-cancer agents, investigators have utilized “maintenance therapy” as a therapeutic strategy in an attempt to delay cancer progression, preserve quality of life and improve survival. This approach would seem to have real potential value for ES-SCLC as patients relapse and become symptomatic very quickly, often so rapidly that they are unable to receive further treatment due to a poor performance status. One of the largest phase III studies in ES-SCLC employed consolidation topotecan (the only FDA approved 2nd line) vs. observation (1). Over 400 patients enrolled and received 4 cycles of cisplatin and etoposide. The 223 patients who demonstrated either a response or stable disease were randomized to immediate topotecan 1.5 mg/m²/day for 5 days of a 21-day cycle for 4 cycles or to observation alone. A modest improvement in median progression free survival (PFS) identified with maintenance topotecan combined with the toxicity profile would not change the current standard of care. Changes in future trial design may enhance the ability to identify agents that will preserve patient functionality and prolong survival.
identified and this approach was not incorporated into standard practice.

In the article accompanying this editorial, Ready et al. present the results from CALGB (Alliance) 30504: a phase II trial that compared sunitinib maintenance treatment to placebo in patients with untreated extensive-stage small-cell lung cancer (ES-SCLC) (2). Sunitinib is a small molecule inhibitor of receptor tyrosine kinases involved in tumor proliferation and angiogenesis, specifically VEGFR, PDGFR, KIT, FLT3 and RET. Preclinical data suggest that angiogenesis is a relevant biological phenomenon in SCLC. Human SCLC cells express functional VEGF receptors and inhibition of VEGFR led to reduced cell growth and migration (3).

The trial initially combined sunitinib with concurrent cisplatin and etoposide; however severe toxicity with neutropenic sepsis prohibited this approach. Subsequent patients received induction chemotherapy with cisplatin 80 mg/m² or carboplatin AUC 5 on day 1 plus etoposide 100 mg/m² days 1-3 of a 21-day cycle for 4-6 cycles. Those without progression were randomized to maintenance sunitinib 37.5 mg per day or placebo until disease progression. Prophylactic cranial irradiation was given in 2.5 Gy fractions to a total dose of 25 Gy and the sunitinib/placebo was held during this treatment. Cross-over to sunitinib was allowed for patients who progressed on the placebo arm. The primary endpoint was PFS from the time of randomization. One hundred forty-four patients enrolled and 138 patients began cisplatin/etoposide with the majority switching over to carboplatin during the course of induction therapy. Eighty-five patients proceeded to the maintenance portion of the study (44 sunitinib, 41 placebo).

The trial met its primary endpoint with an improvement in PFS (3.7 vs. 2.1 months; HR =1.62; 95% CI, 1.02-2.60; one-sided P=0.02). Median OS from the time of randomization also favored maintenance sunitinib (9.0 vs. 6.9 months), but this difference was not statistically significant. Grade 3 toxicity with sunitinib included fatigue (19%), neutropenia (14%) and thrombocytopenia (7%).

Are these results meaningful to our ES-SCLC patients and should we consider this as a potential treatment option for those who respond to induction chemotherapy? To answer this, three questions need to be addressed: (I) Is PFS a clinically meaningful endpoint? (II) If so, is a 1-2-month improvement in PFS clinically meaningful? (III) And if so, does the clinical benefit outweigh the potential side effects?

(I) Is PFS a clinically meaningful endpoint? It must be acknowledged that the authors conducted a very well designed trial that allowed standard of care therapy (including prophylactic cranial irradiation) and avoided pitfalls of other maintenance trials such as not ensuring access to the experimental therapy for the patients on the placebo arm (4). ES-SCLC is a reasonable disease to investigate agents that delay tumor progression given that rapid disease growth almost uniformly produces distressing symptoms like shortness of breath, pain and fatigue. Improvement in PFS would be a meaningful endpoint if it is associated with an improvement in quality of life. Unfortunately, these data are lacking in this trial, so it is unclear if this improvement in PFS was associated with reduction in symptom burden or improvement in performance status. Although it is challenging to conduct and analyze quality of life studies in this patient population, we owe it to them to ensure our statistical improvements translate into improved functionality. A modest improvement in PFS without improvement in quality of life is not meaningful.

(II) Is a 1.6-month improvement in PFS clinically meaningful? The American Society of Clinical Oncology (ASCO) recently issued a challenge to “raise the bar” for clinical trials by defining the magnitude of meaningful outcomes (5). ASCO convened working groups in major tumor types (including lung cancer) to propose the design of future clinical trials that would achieve clinically meaningful results for our patients. This was not intended to “set the standard” of future clinical trials, but to encourage investigators and patients to expect clinically meaningful results. The working groups acknowledged that we should see “extremely strong signals in phase II studies” to expect meaningful results for our patients. This was not acknowledged that the authors conducted a very well designed trial that allowed standard of care therapy (including prophylactic cranial irradiation) and avoided pitfalls of other maintenance trials such as not ensuring access to the experimental therapy for the patients on the placebo arm (4). ES-SCLC is a reasonable disease to investigate agents that delay tumor progression given that rapid disease growth almost uniformly produces distressing symptoms like shortness of breath, pain and fatigue. Improvement in PFS would be a meaningful endpoint if it is associated with an improvement in quality of life. Unfortunately, these data are lacking in this trial, so it is unclear if this improvement in PFS was associated with reduction in symptom burden or improvement in performance status. Although it is challenging to conduct and analyze quality of life studies in this patient population, we owe it to them to ensure our statistical improvements translate into improved functionality. A modest improvement in PFS without improvement in quality of life is not meaningful.

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maintenance sunitinib appear to fall short of these goals.

(III) Does the clinical benefit outweigh the potential toxicity? The ASCO working groups also noted that treatment-related toxicity should help dictate the level of meaningful clinical benefit (a modest benefit may be acceptable for low toxic agents, but robust clinical benefit is required for agents with higher toxic potential). This relates to the third question of the toxicity of sunitinib in patients with SCLC who have been heavily pretreated with induction chemotherapy. It should be noted that the patients randomized on this study represent the “good actors,” meaning that patients with chemorefractory disease or declining performance status were not eligible for randomization. Despite this, toxicity was not trivial as 21 of the 44 patients receiving sunitinib required dose reductions. Fifty-four percent experienced grade 3/4 toxicity and 19% developed grade 3 fatigue that is defined as “fatigue not relieved by rest and limits self-care activities of daily living” (6). The toxicities in this study are consistent with other maintenance sunitinib trials for ES-SCLC that concluded this was a tough agent to administer safely. Two single-arm phase II maintenance trials employed a different dose and schedule of sunitinib (50 mg daily for 4 weeks of a 6-week cycle). Our study found no clinical benefit with maintenance sunitinib and noted that half of patients discontinued the agent due to toxicity or requested to stop therapy (7). The second study reported a median PFS of 1.4 months in 24 patients treated with maintenance sunitinib (8). Again, grade 3/4 toxicities included thrombocytopenia (63%), asthenia (29%), and neutropenia (25%), and 75% of patients required dose interruptions. The authors concluded that this approach did not warrant further investigation given the toxicity and low PFS. Clearly, sunitinib is a tough drug in this population and it is unlikely that the reported benefits would outweigh the risks.

So what is the next step? The authors conclude that a randomized phase II study with OS as the primary endpoint and incorporation of correlative evaluation of potential biomarkers that could predict benefit of sunitinib would be warranted. This would be reasonable if quality of life measures were also incorporated given the significant toxicity and modest benefit identified in the current study. However, biomarkers to predict benefit from antiangiogenic agents have been extremely difficult to identify.

CALGB 30504 does not change the standard of care for patients with newly diagnosed ES-SCLC. Four to six cycles of platinum-based chemotherapy remains the optimal frontline treatment without maintenance therapy. Given the modest improvement in PFS and potential toxicity, maintenance sunitinib should not be offered to patients as a potential treatment option unless it is part of a clinical trial. This study is an encouraging step in the right direction towards better care for ES-SCLC patients. The concept of maintenance therapy, the rational study design and the careful execution of the trial in patients with this often underserved disease is commendable. However, future SCLC maintenance studies should evaluate quality of life parameters and incorporate clinically meaningful endpoints outlined by ASCO. This will enhance the ability of maintenance trials to effectively demonstrate both an improvement in functionality and prolongation of survival for patients with this difficult disease.

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Footnote

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References


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