Paclitaxel Plus Bevacizumab Is a Feasible Option for Chemoresistant SCLC

Written by Jenny Powers

Salvage treatment combining paclitaxel and bevacizumab was feasible and improved outcomes in heavily pretreated patients with advanced, chemoresistant small cell lung cancer (SCLC) in a small single-center study conducted by the Hellenic Oncology Research Group. Safety concerns were an issue with these patients, who had poor prognoses and few treatment options, explained Giannis Mountzios, MD, University of Athens School of Medicine, Athens, Greece.

During this Phase 2 multicenter study, researchers evaluated the efficacy and tolerance of treatment with paclitaxel plus bevacizumab in patients with SCLC who relapsed after chemotherapy. Prof. Mountzios explained that the rationale behind the combination was that SCLC is a highly aggressive cancer, and many patients may also have distal metastasis. Although chemotherapy (CT) is the treatment of choice for all stages of SCLC, these patients had already shown resistance to it. Single-agent paclitaxel as the

Table 1. Adverse Events Deemed Possibly Treatment Related, Grades 1 to 4

	Grade 1		Grade 2		Grade 3		Grade 4	
	n	%	n	%	n	%	n	%
Leukopenia	6	20.0	7	23.3	5	16.7	1	3.3
Neutropenia	5	16.7	6	20.0	4	13.3	1	3.3
Febrile neutropenia	—	—	—	—	1	3.3	—	—
Anemia	19	63.3	7	23.3	1	3.3	—	—
Thrombocytopenia	7	23.3	2	6.7	—	—	—	—
Nausea	3	10.0	—	—	1	3.3	—	—
Vomiting	2	6.7	—	—	1	3.3	—	—
Diarrhea	2	6.7	1	3.3	1	3.3	2	6.7
Mucositis	3	10.0	1	3.3	—	—	—	—
Constipation	1	3.3	—	—	—	—	—	—
Neurotoxicity	1	3.3	4	13.3	—	—	—	—
Edema	1	3.3	—	—	—	—	—	—
Fever	1	3.3	—	—	—	—	—	—
Hypertension	10	33.3	—	—	—	—	—	—
Proteinuria	4	13.3	—	—	—	—	—	—
Pulmonary hemorrhage	2	6.7	—	—	—	—	—	—
Fatigue	7	23.3	9	30.0	—	—	1	3.3

first-line therapy had shown benefit in 36 patients with extensive-disease SCLC in a Phase 2 trial performed by the Eastern Cooperative Oncology Group (ECOG); although no complete response was observed, 11 (34%) patients had a partial response, and 6 (19%) achieved stable disease, of whom one-half showed tumor shrinkage of 50% or more [Ettinger DS et al. *J Clin Oncol* 1995].

Responses were observed. A Phase 2 trial of second-line paclitaxel in 21 patients with relapsed and refractory SCLC demonstrated a response rate of 23.8% with 5 (23.8%) patients achieving partial response [Yamamoto N et al. *Anticancer Research* 2006]. Bevacizumab was added because angiogenesis seems to play an important role in SCLC progression [Lucchi M et al. *Eur J Cardiothoracic Surg* 2002].

This Phase 2 multicenter study enrolled 30 patients with SCLC and an ECOG Performance Status of 0 to 2 who experienced relapse within 3 months after completing first-line chemotherapy. All patients received paclitaxel (90 mg/m^2 on days 1, 8, and 15) plus bevacizumab (10 mg/kg on Days 1 and 15) in 28-day cycles.

The majority (90%) of the patients were men, the median age was 64 years, and 9 (30%) had brain metastases at study entry. Previous treatment included 2 or more lines of CT in 19 (63.3%) patients and radiotherapy in 17 (56.7%) patients.

The overall objective response rate was 20% (95% CI, 5.69% to 34.31%), and the disease control rate was 36.7%.

The median overall survival was 6.3 months (95% CI, 3.1 to 9.4; range, 0.5 to 17.9). The median time to progression was 11 weeks (range, 2 to 37). The 1-year overall survival rate was 25.4%.

At the end of an 18-month follow-up, 1 patient was lost to follow-up and 29 patients experienced disease progression, of whom 26 had died.

Patients received a median of 3 (range, 1 to 6) chemotherapy cycles; a total of 84 treatment cycles were administered.

Treatment delay occurred for 18 (21.4%) cycles, and subsequent dose modifications were made due to myelosuppression (especially neutropenia), diarrhea, mucositis, neurotoxicity, and fatigue. All possibly treatment-related adverse events (grades 1 to 4) are listed in Table 1.

Disease progression was cited as the cause for 73% of treatment interruptions; 3 treatment interruptions were due to unacceptable toxicity.

One nonfatal pulmonary embolism occurred that could possibly have been bevacizumab related.

Prof. Mountzios commented on the safety results, saying that this treatment has an advantage of combining a cytotoxic agent with a biological agent that results in the same types of toxicities. He suggested that this combination showed promising results compared with topotecan—the current standard second-line chemotherapy for SCLC—that warrant validation and further study in a larger patient cohort.

Topotecan has shown longer survival when administered with best supportive care (BSC) compared with BSC administered alone in a Phase 3 trial of patients with relapsed SCLC; median overall survival in 71 topotecan-treated patients was 25.9 weeks compared with 13.9 weeks in 70 patients receiving BSC (log-rank p=0.0104) [O'Brien ME et al. *J Clin Oncol* 2006]. A Phase 3 trial comparing second-line oral and intravenous (IV) topotecan in patients with measurable recurrent SCLC following first-line treatment showed response rates of 18.3% in 153 patients given oral topotecan compared with 21.9% of patients receiving IV topotecan. Response rates for third-line oral and IV topotecan were 33% and 35%, respectively [Eckart JR. *J Clin Oncol* 2007].

No Significant Difference in Treatment Versus Supportive Care in Stage IV NSCLC

Written by Rita Buckley

Researchers in Egypt conducting a prospective, Phase 3, randomized trial found no significant difference in time to progression (TTP) or overall survival (OS) in patients with stage IV advanced and metastatic non–small cell lung cancer (NSCLC) who received either gemcitabine or best supportive care (BSC) after induction therapy. Findings were displayed in a poster presentation.

Maintenance therapy in NSCLC has been extensively investigated. Evidence suggests that first-line cytotoxic combination chemotherapy should be stopped at disease progression or after 4 cycles in patients whose disease is nonresponsive to treatment [Brodowicz T et al. *Lung Cancer* 2006; Park JO et al. *J Clin Oncol* 2007; Socinski MA et al. *J Clin Oncol* 2002; von Plessen C et al. *Br J Cancer* 2006].

Pretrexed continuation maintenance therapy is well tolerated and offers superior OS compared with placebo [PARAMOUNT (NCT00102804); Paz-Ares L et al. *Lancet Oncol* 2012], and maintenance therapy with erlotinib produced significantly longer progression-free survival [A Study of Tarceva (Erlotinib) Following Platinum-Based Chemotherapy in Patients With Advanced, Recurrent, or