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

Metastatic Non–Small Cell Lung Cancer (NCT00556712); Cappuzzo F et al. *Lancet Oncol* 2010].

The purpose of this study, which was conducted by the Clinical Oncology and Nuclear Medicine Department at Ain Shams University Hospitals in Cairo, Egypt, was to evaluate the efficacy—defined as prolongation of TTP, OS, and safety (grade 3 or 4 toxicity)—of low-dose gemcitabine as maintenance chemotherapy after first-line gemcitabine and cisplatin in advanced and metastatic NSCLC.

A total of 120 patients with advanced NSCLC presented at the Clinical Oncology and Nuclear Medicine Department at Ain Shams University Hospitals between January 2010 and June 2012. Of these, 75.5% were male, 70% were younger than 60 years, 59.2% had performance status (PS) 2, 2.75% had nonsquamous histology, and 79.2% had stage IV disease. All eligible patients received induction chemotherapy with gemcitabine and cisplatin.

Patients who completed 4 cycles and showed complete response, partial response, or stable disease were randomized into two arms: (1) gemcitabine 250 mg/m^2 given throughout 6 hours on days 1 and 8 every 3 weeks, or (2) BSC. Responses were assessed according to Response Evaluation Criteria in Solid Tumors guidelines every 2 cycles.

After each cycle, toxicities were evaluated according to National Cancer Institute criteria for common toxicities. Patients with progressive disease (PD) were excluded from the study, as were those who did not finish 4 cycles and showed doubling time, PD, or toxicity.

Results showed a median TTP of 6.1 months (CI, 5.3 to 6.6; p=0.454) in arm I and 5.8 months (CI, 5.2 to 6.4; p=0.454) in arm II. The median OS was 9 months (CI, 7.9 to 10.0; p=0.994) in arm I and 8 months (CI, 8.5 to 9.4; p=0.994) in arm II. The trial showed that maintenance therapy was well tolerated, with no grade 3 or 4 toxicity. The only significant finding was grade 2 anemia in 8 patients (22.9%) in the maintenance arm (arm I).

The clinical trial failed to show any statistical significance in TTP or OS between the 2 arms. The authors report that this could be due to the smaller sample size or the use of low-dose rather than conventional-dose gemcitabine. Other factors might include the predominance of nonsquamous histology and PS 2.

Evidence-based data indicate that this analysis of study outcomes is accurate. PS is among the most important prognostic factors for survival with NSCLC [Sweeney CJ et al. *Cancer* 2001]. PS, histology, and age versus comorbidity are the principal determinants of first-line treatment with cytotoxic combination chemotherapy, including platinum with gemcitabine. Treatment goals are to prolong survival and control disease-related symptoms. First-line treatment with platinum combinations, such as gemcitabine, yields similar improvements in survival [National Cancer Institute online 2014].

Benefit and Tolerance to Induction Therapy in Elderly Patients With Locally Advanced NSCLC

Written by Jenny Powers

Elderly patients with locally advanced non--small cell lung cancer (NSCLC) could present similar benefit and tolerance as their younger counterparts to induction chemotherapy (CT) or chemoradiotherapy (CRT) followed by either surgical resection or consolidation radiotherapy. Dr. Diego Márquez-Medina, University Hospital Arnau de Vilanova, Lleida, Spain, noted the conundrum that the elderly population is growing and that half of lung cancers are diagnosed in patients older than 60 years [Gridelli C et al. *Crit Rev Oncol Hematol* 2002]. However, elderly patients are seldom included in multimodal programs of induction CT or CRT [Gridelli C et al. *Crit Rev Oncol Hematol* 2002].

The Spanish investigators conducted a retrospective review of data from 108 consecutive patients with Eastern Cooperative Oncology Group status 0 to 2 locally advanced NSCLC who received induction CT or CRT plus surgery or consolidation radiotherapy, analyzing the feasibility, tolerability, and efficacy of these therapies in patients younger (59.2%) and older (40.7%) than 70 years. Elderly patients tended to present worse Eastern Cooperative Oncology Group scores (p=0.088) and stage IIIB NSCLC. The prevalence rates of squamous cell carcinomas, adenocarcinomas, and unspecified NSCLC were similar between the cohorts.

The CT regimens included platinum doublets with vinorelbine, gemcitabine, and taxanes. Carboplatin doublets were more commonly administered to the elderly patients (p=0.025).

Induction CRT and CT were administered to 59.3% and 40.7% of younger and 49.9% and 50.1% of older patients, respectively. Both age groups had similar radiologic responses. Pathologic responses after resection surgery were also similar between age groups, and no differences regarding overall survival and disease-free survival were found. Interestingly, grade 3 or 4 toxicity was more common among younger patients (p=0.053). No grade 3 or 4 pneumonitis was detected in either age group.